Marqueurs Moléculaires de Réponse à la Chimiothérapie

Jean-Paul Borg
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Inserm
Institut national
de la santé et de la recherche médicale

INSTITUT
CENTRE REGIONAL DE LUTTE CONTRE LE CANCER
PAOLI-CALMETTES
PROVENCE - ALPES - CÔTE D'AZUR

ÉQUIPE LABELLISÉE PAR LA LIGUE CONTRE LE CANCER
CONTRE LE CANCER
LA LIGUE
101 comités

canceropôle
Provence-Alpes-Côte d'Azur

Lab. of Molecular Pharmacology
Jean-Paul Borg, Group leader

Cell Signaling & Cancer
Jean-Paul Borg, DR Inserm

Marie-Josée Santoni, CR1 CNRS
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Two-Hybrid in yeast
Patrick Lécine, CR1 Inserm

Aurélie Hermant, tech Cancéropole

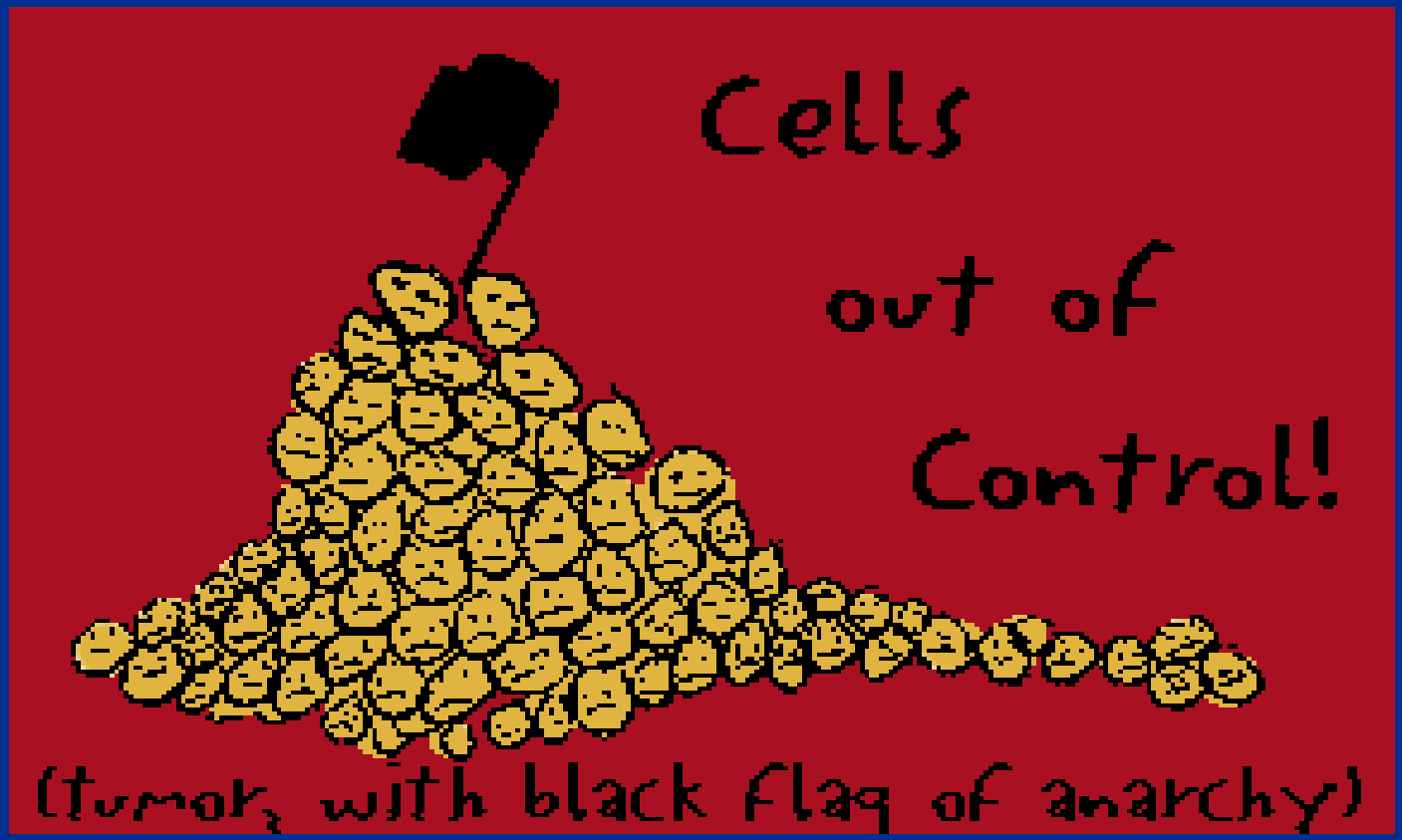
Proteomics
Stéphane Audebert, Ingénieur IPC

Christine Sempéré, tech IPC

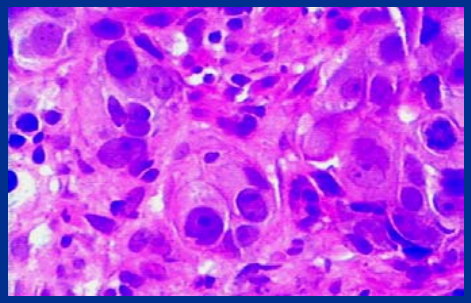
Caractériser les mécanismes moléculaires impliqués dans la cancérisation des tissus

Identifier de nouvelles cibles thérapeutiques

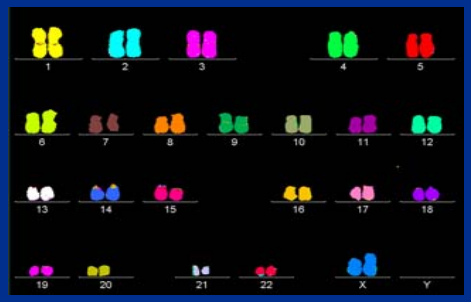
Optimiser les thérapeutiques


Cells
out of
Control!
(tumor, with black flag of anarchy)

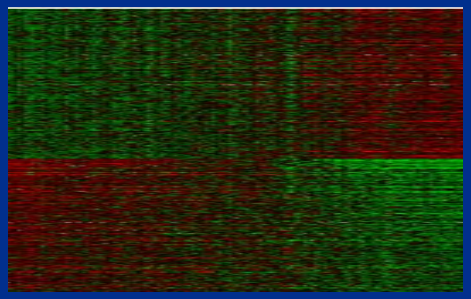
Vers une définition moléculaire de la maladie



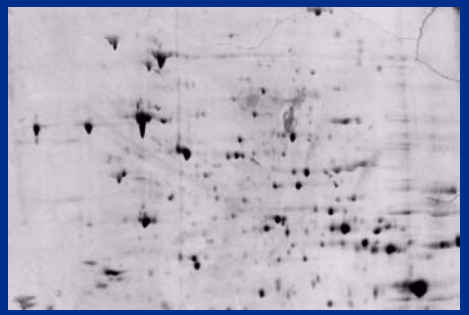
Morphologie



Chromosomes



Gènes



Protéines

Cells

ECM

In

Growth Factors (e.g. TGFα)

RTK

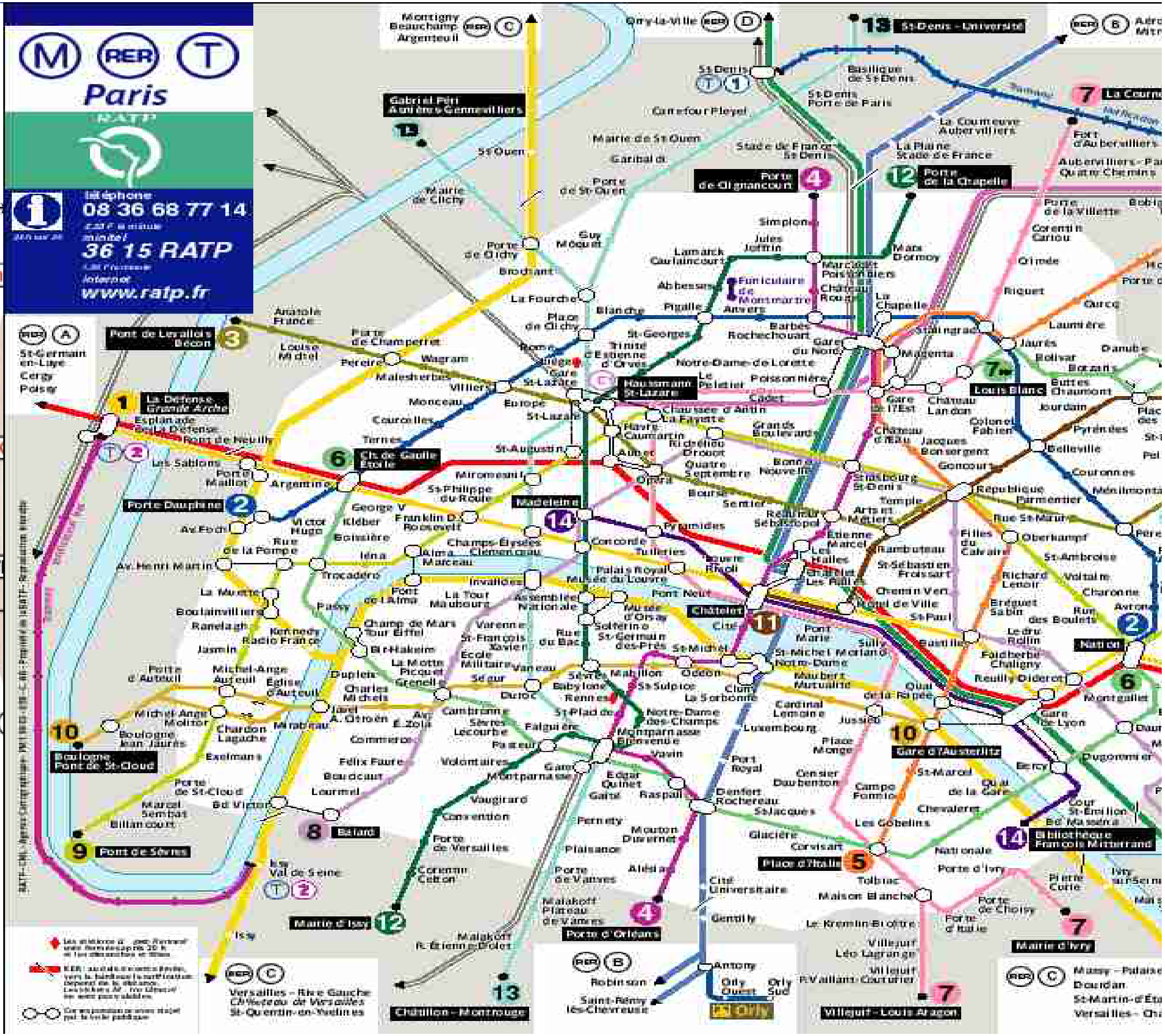
Hormones

(e.g. Bombesin)

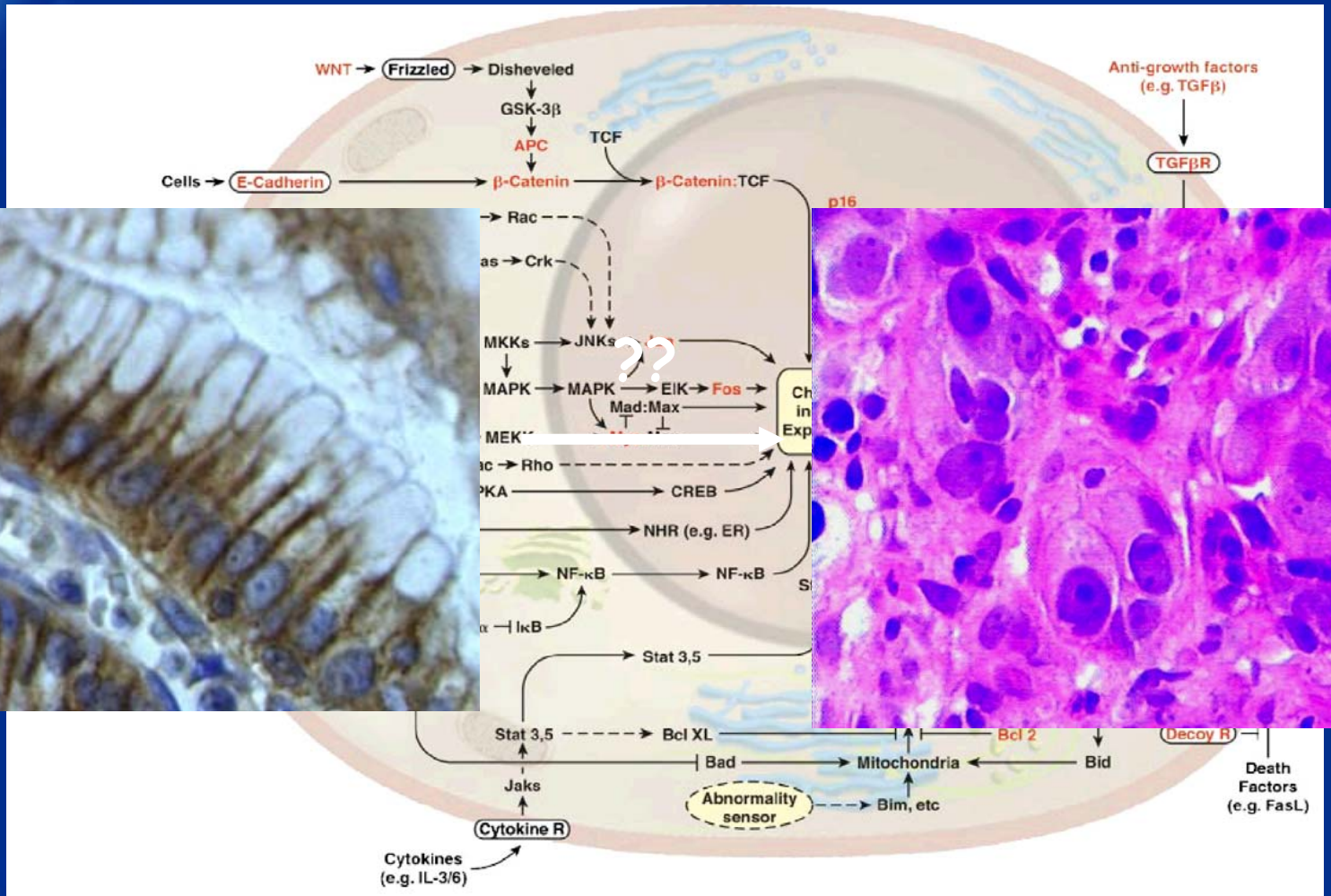
7-T

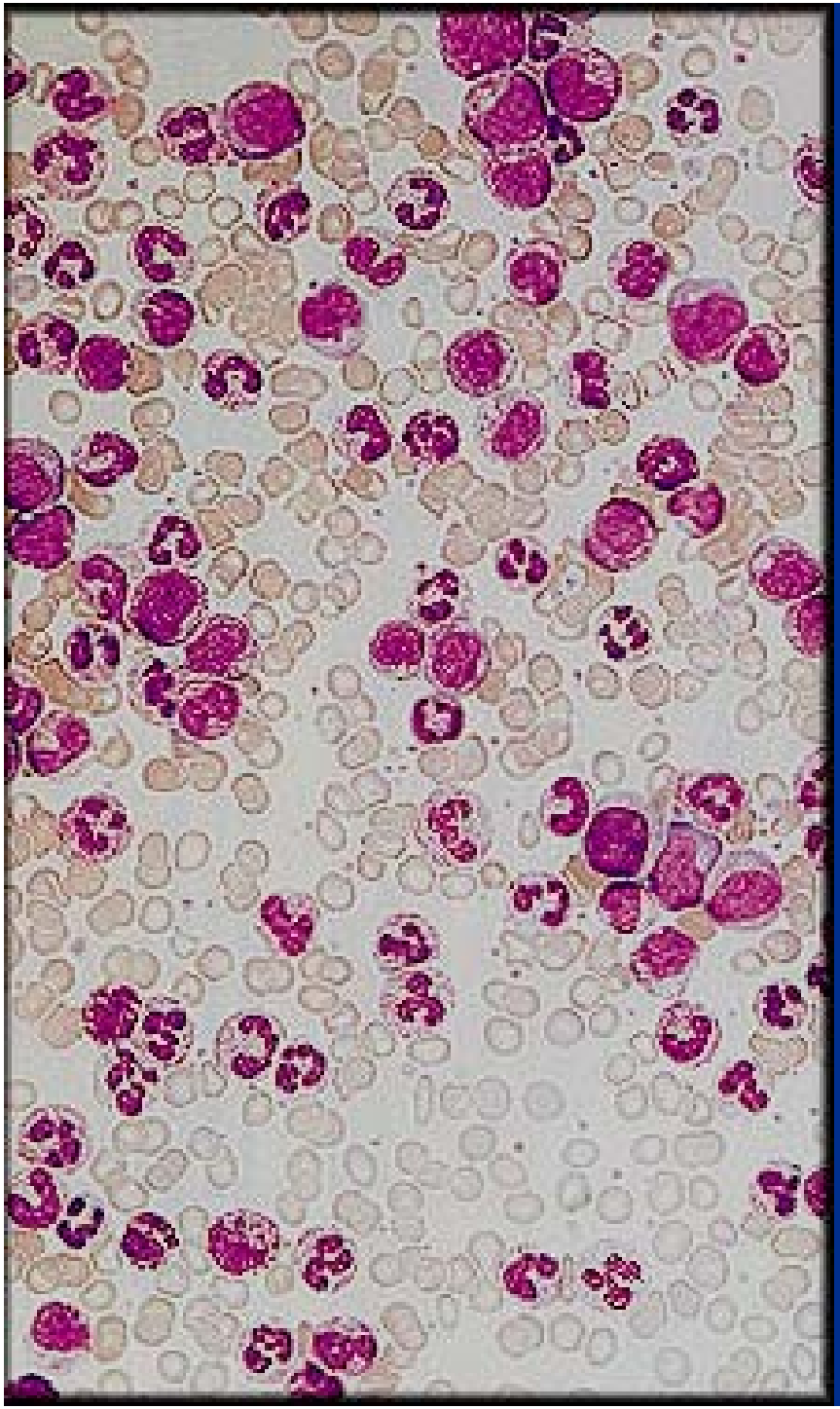
(e.g. Estrogen)

Survival Factors (e.g. IGF1)

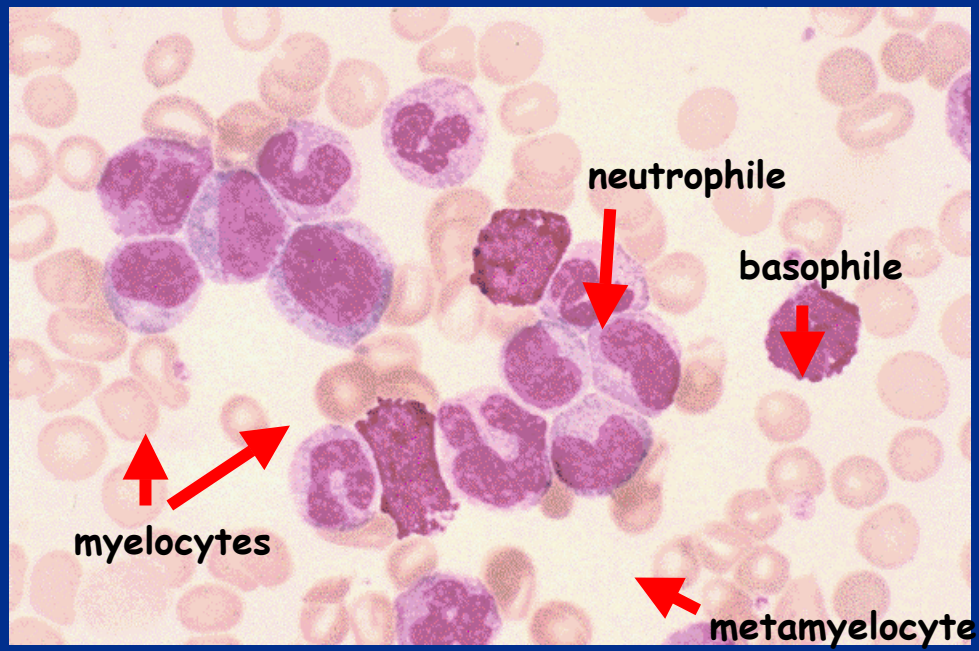


Recherche cognitive: pour faire quoi?

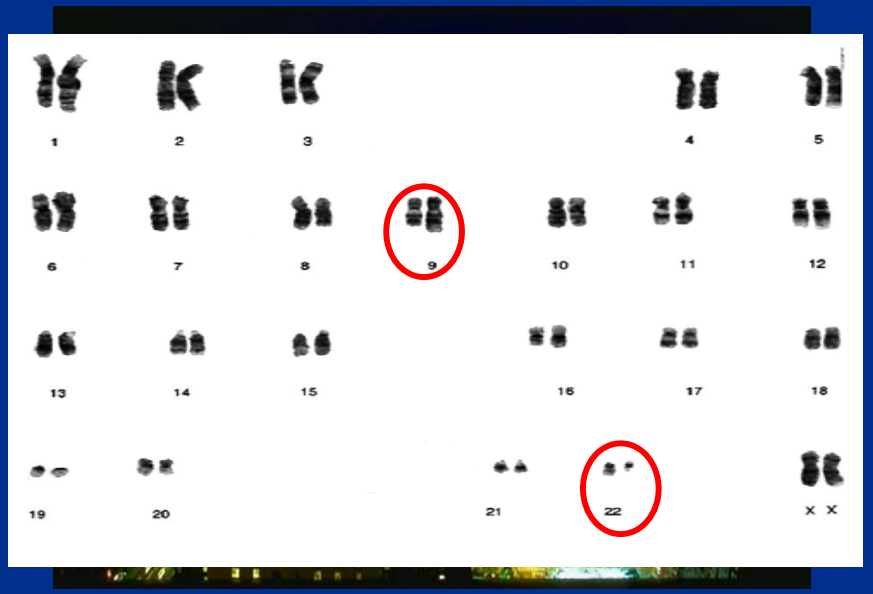




Leucémie Myéloïde Chronique



The Philadelphia Chromosome

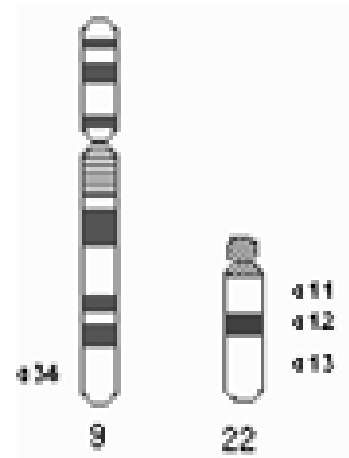


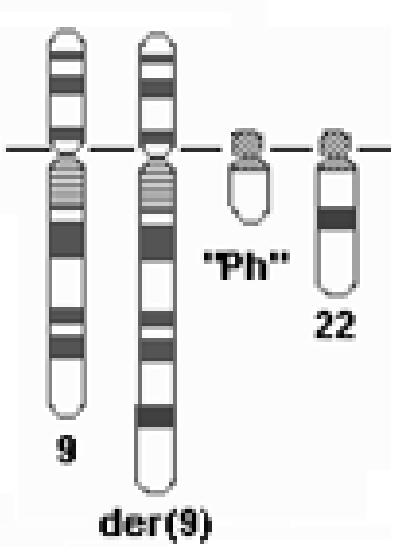
"The findings suggest a causal relationship between the chromosome abnormality observed and chronic granulocytic leukemia."

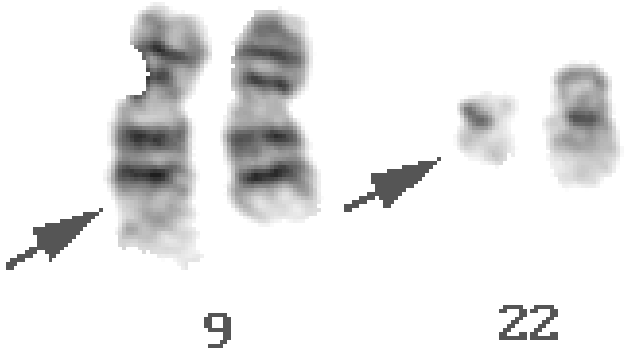
P. Nowell-1960

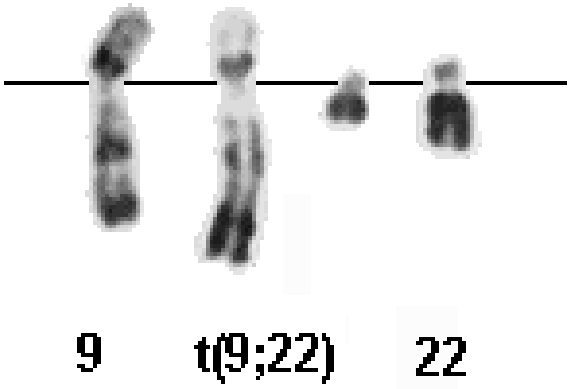
Janet Rowley

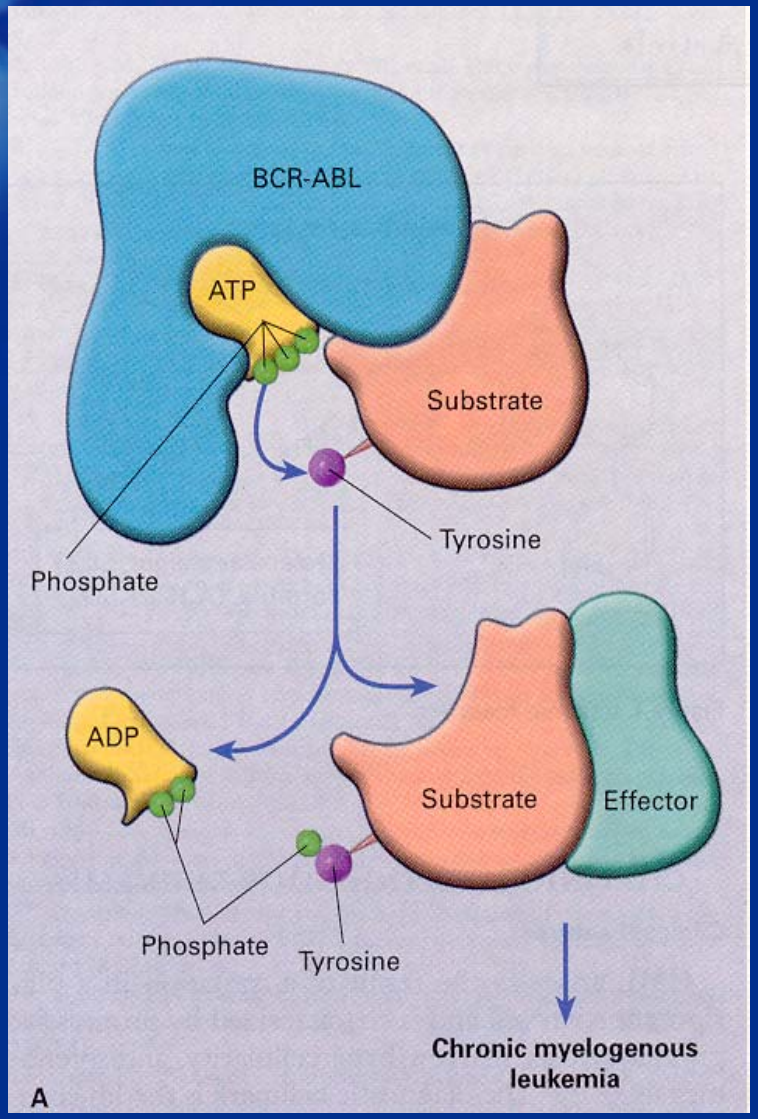
1973

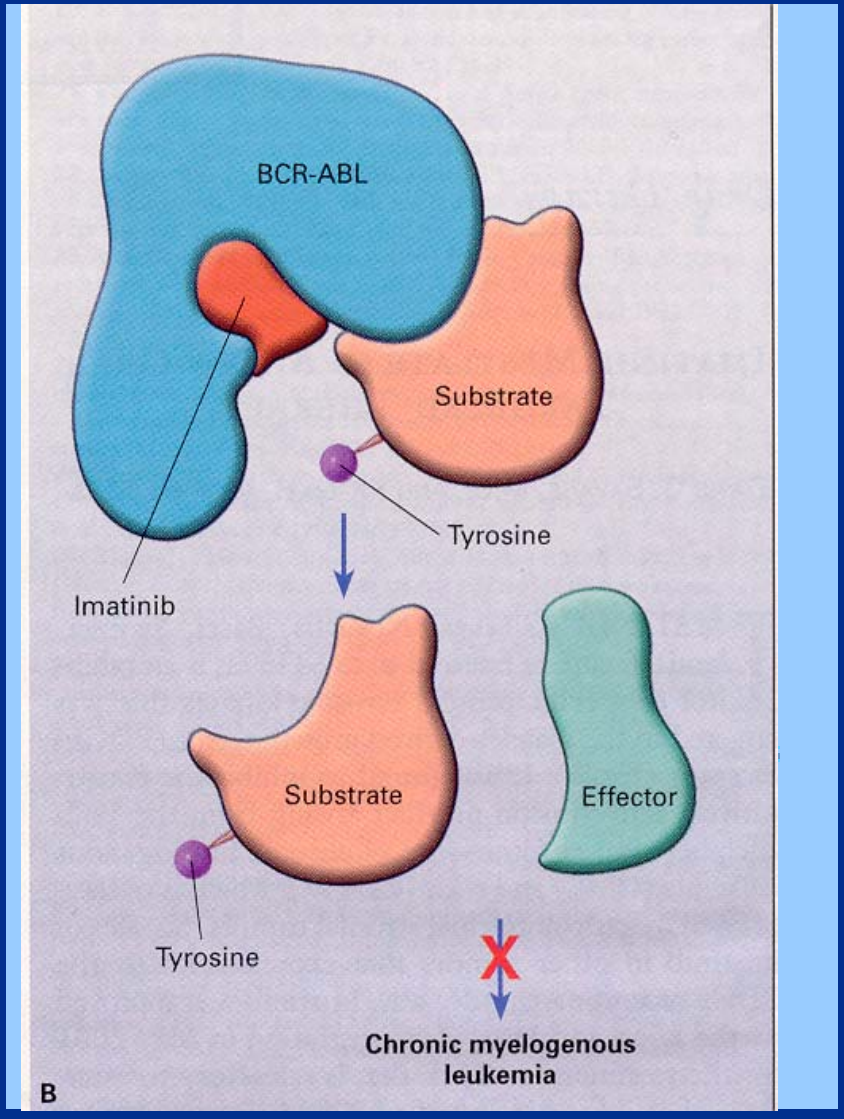




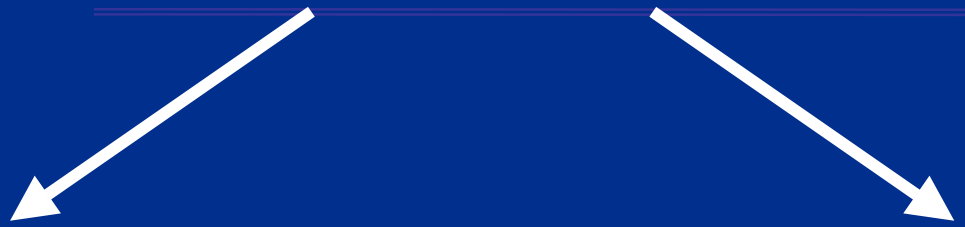





BCR-ABL
ATP
Substrate
Tyrosine
Phosphate
ADP
Substrate
Effector
Phosphate
Tyrosine
Chronic myelogenous leukemia
A


BCR-ABL
Substrate
Tyrosine
Imatinib
Substrate
Effector
Tyrosine
Chronic myelogenous leukemia
B

Resistance to imatinib



Overexpression of the target (BCR-ABL)

Loss of binding to the target (mutations in BCR-ABL)

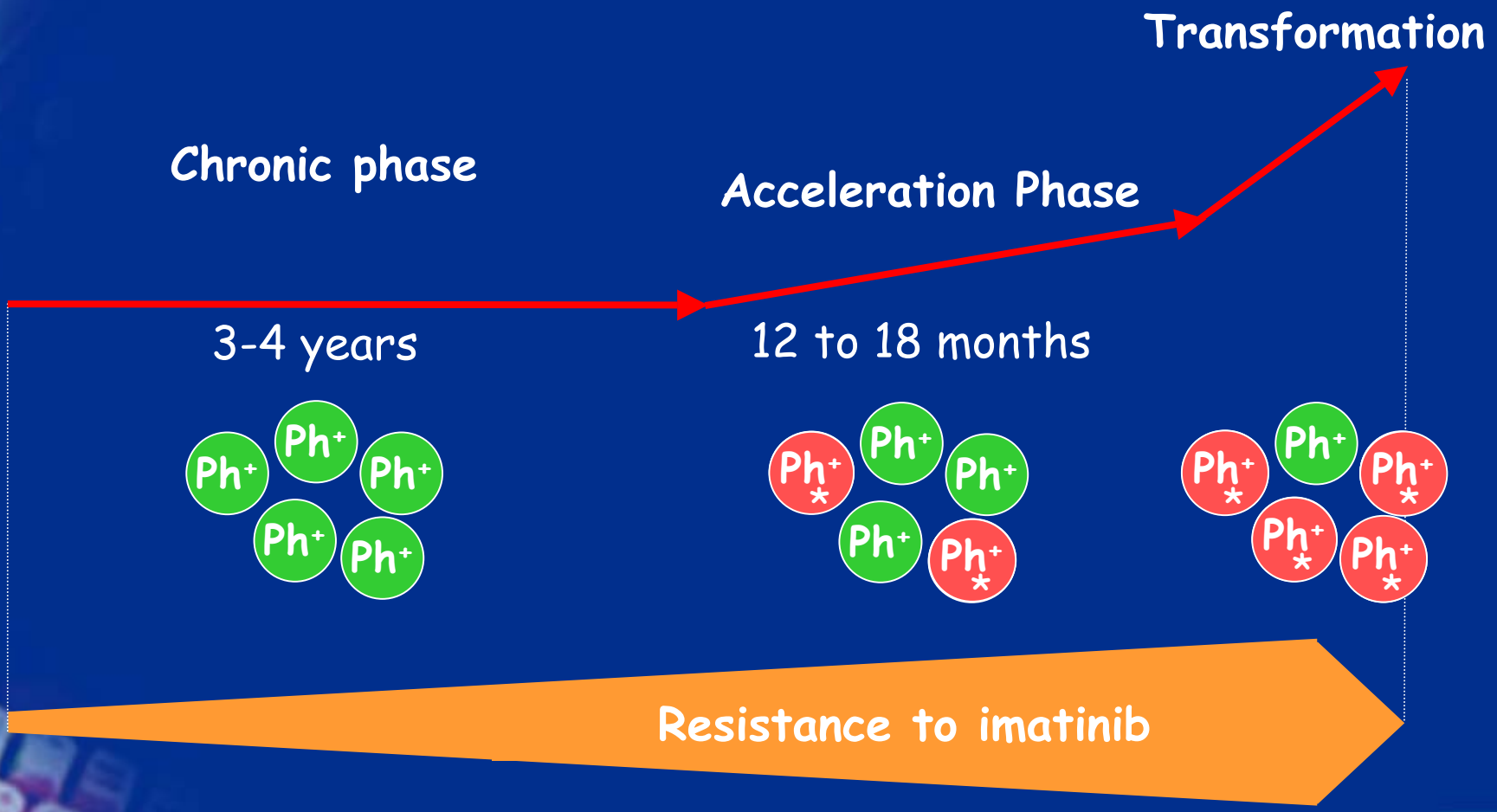
BCR-ABL point mutations associated with imatinib resistance

- A total of 114 mutational events were reported in 179 patients
(some cases exhibiting more than one type of mutation)

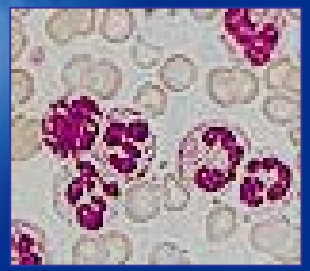
- Point mutations in the kinase domain account for approximately 60% of the cases where lack or loss of response to imatinib is observed in the patients.

Shah NP *et al*, *Cancer Cell* 2002; 2: 117.
Hochhaus A *et al*, *Leukemia* 2002; 16: 2190-2196.
Branford S *et al*, Blood 2002; 98(11):769a-770a.
von Bubnoff N *et al*, *Lancet* 2002; 359: 487-491.
Barthe C *et al*, *Science* 2001; 293: 2163.
Hofmann WK *et al*, *Blood* 2002; 99: 1860-1862.
Roche-Lestienne C *et al*,*Blood* 2002; 100: 1014-1018.

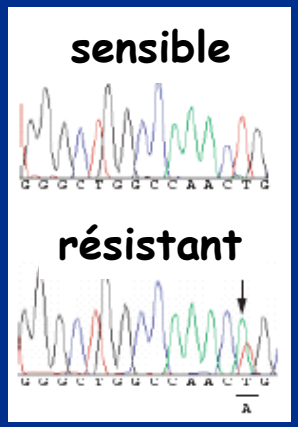
Resistance to imatinib and disease phases

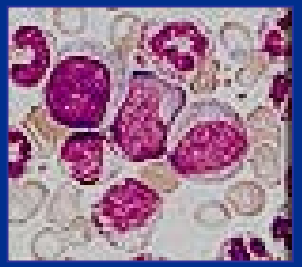


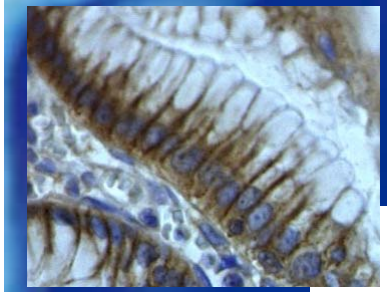
Leucémie Myéloïde Chronique: une seule anomalie cytogénétique



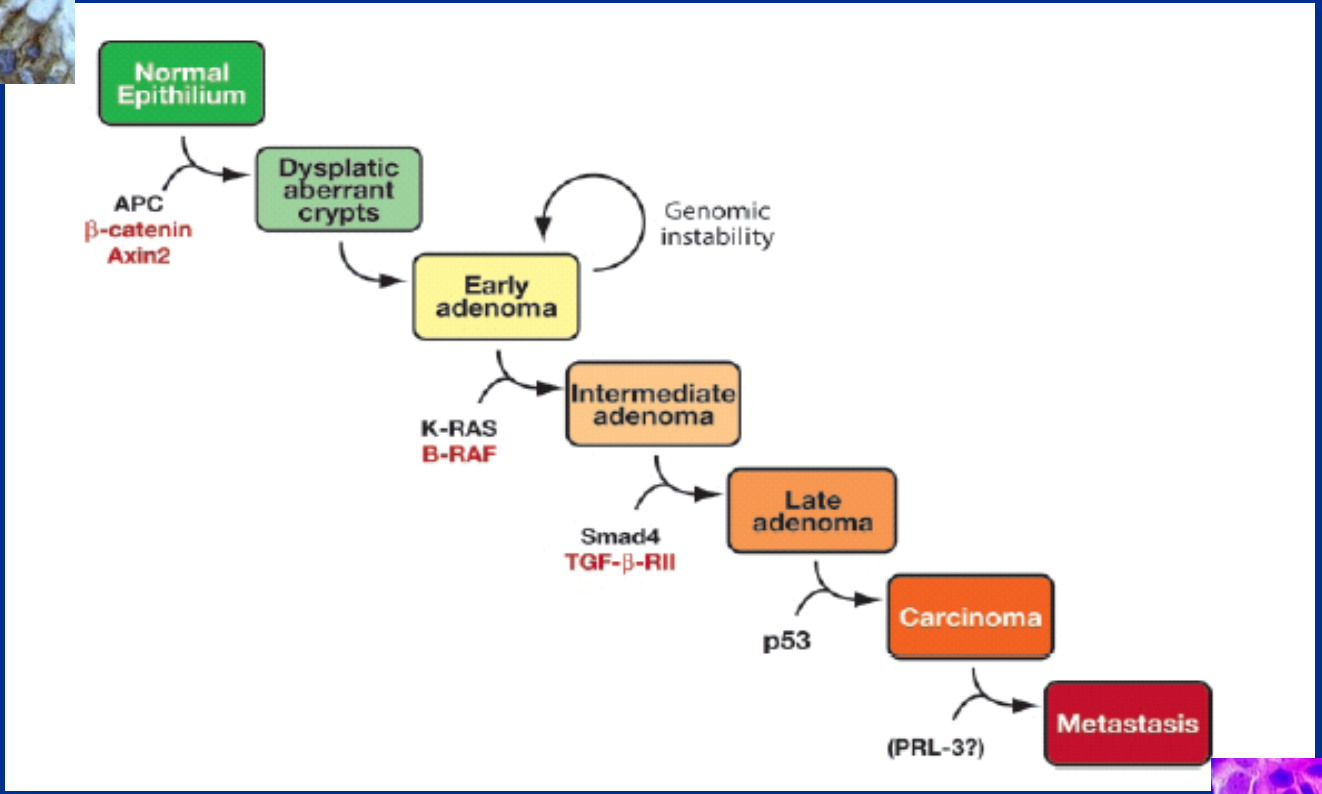
BCR-ABL

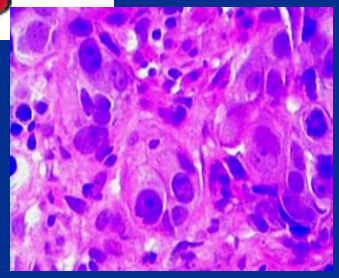






Tumeurs solides: accumulation de mutations



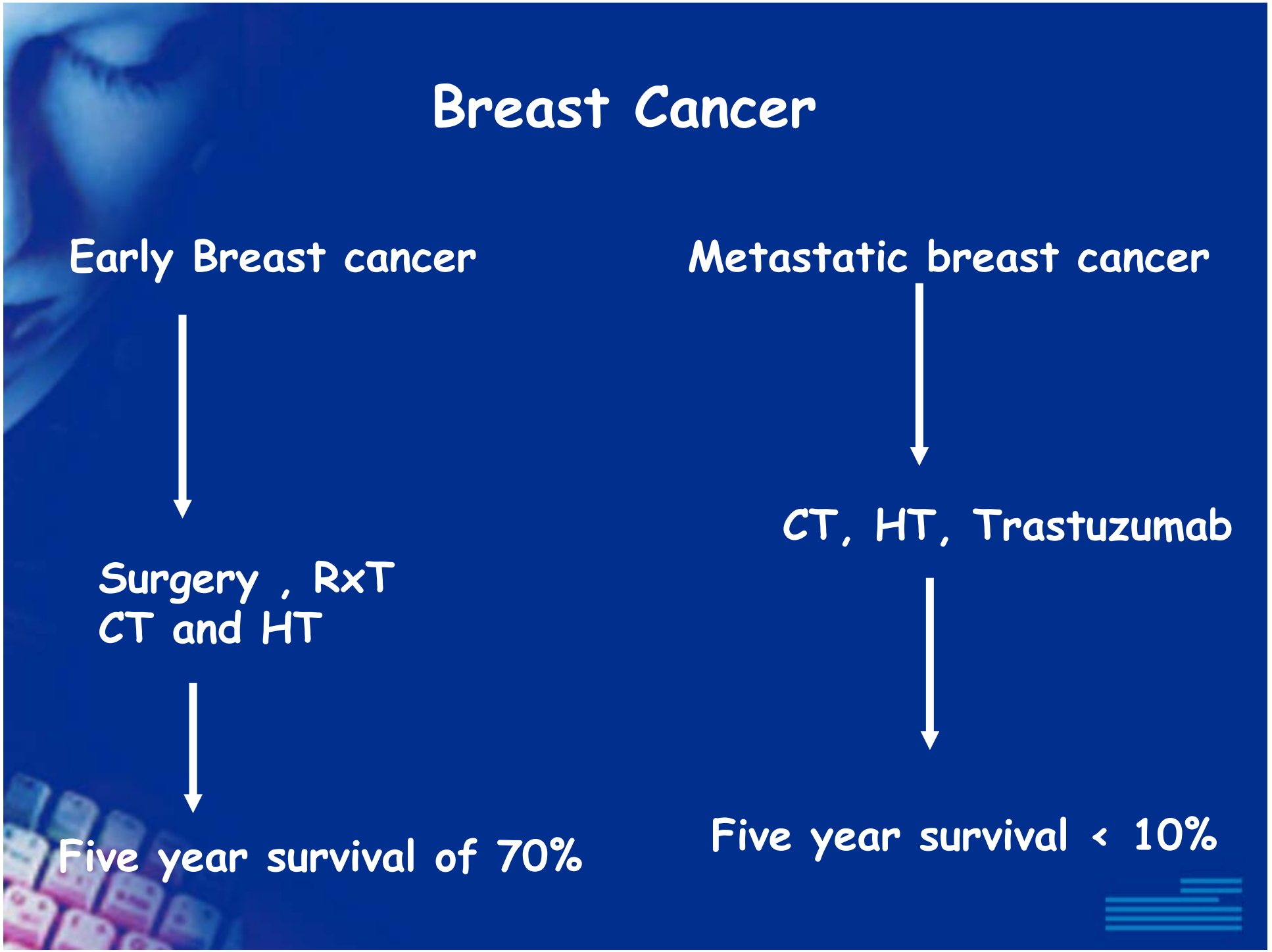


Breast Cancer

cause of death in women between 50 and 69

- > 12000 deaths /year

Breast Cancer



Early Breast cancer

Surgery , RxT
CT and HT

Five year survival of 70%

Metastatic breast cancer

CT, HT, Trastuzumab

Five year survival < 10%

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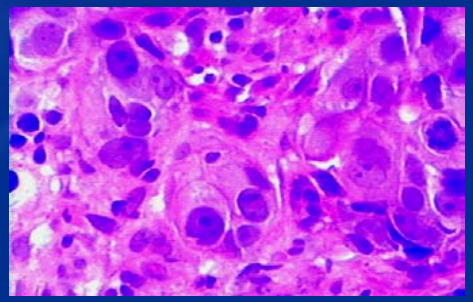
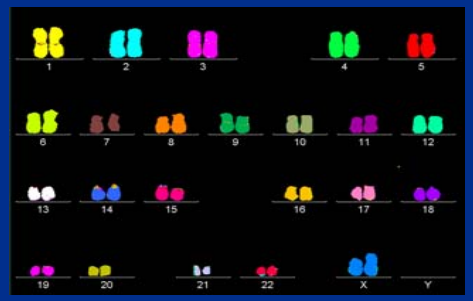
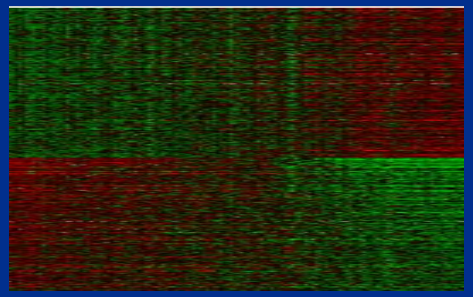
How to optimize the
treatments ?



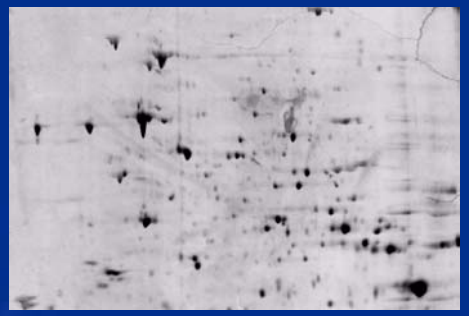
Morphologie



Chromosomes



Gènes



Protéines

Herceptin

Early Breast Cancer

Lymph node invasion
ER/PR
Tumor size
SBR Grade
age

« Good risk »

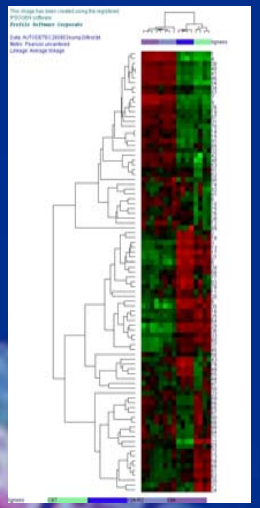
<20% of metastatic relapse

« Poor risk »

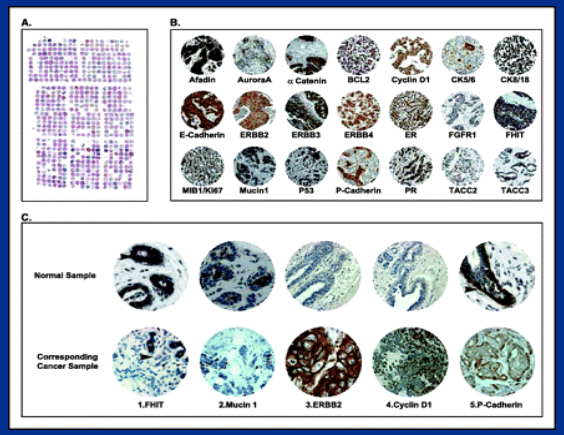
Up to >50% of treatment failure

Panoramical views of expressed genes in biological samples

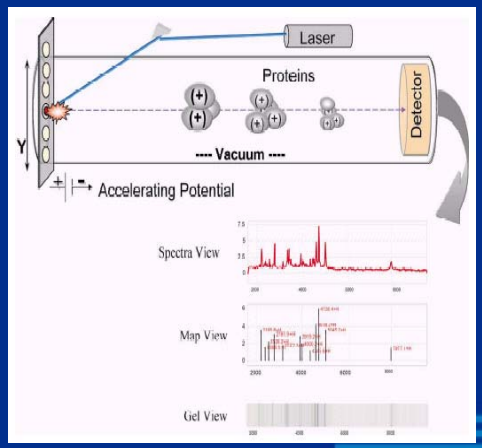
Profil Transcriptionnel Tumoral (Puces a ADN)



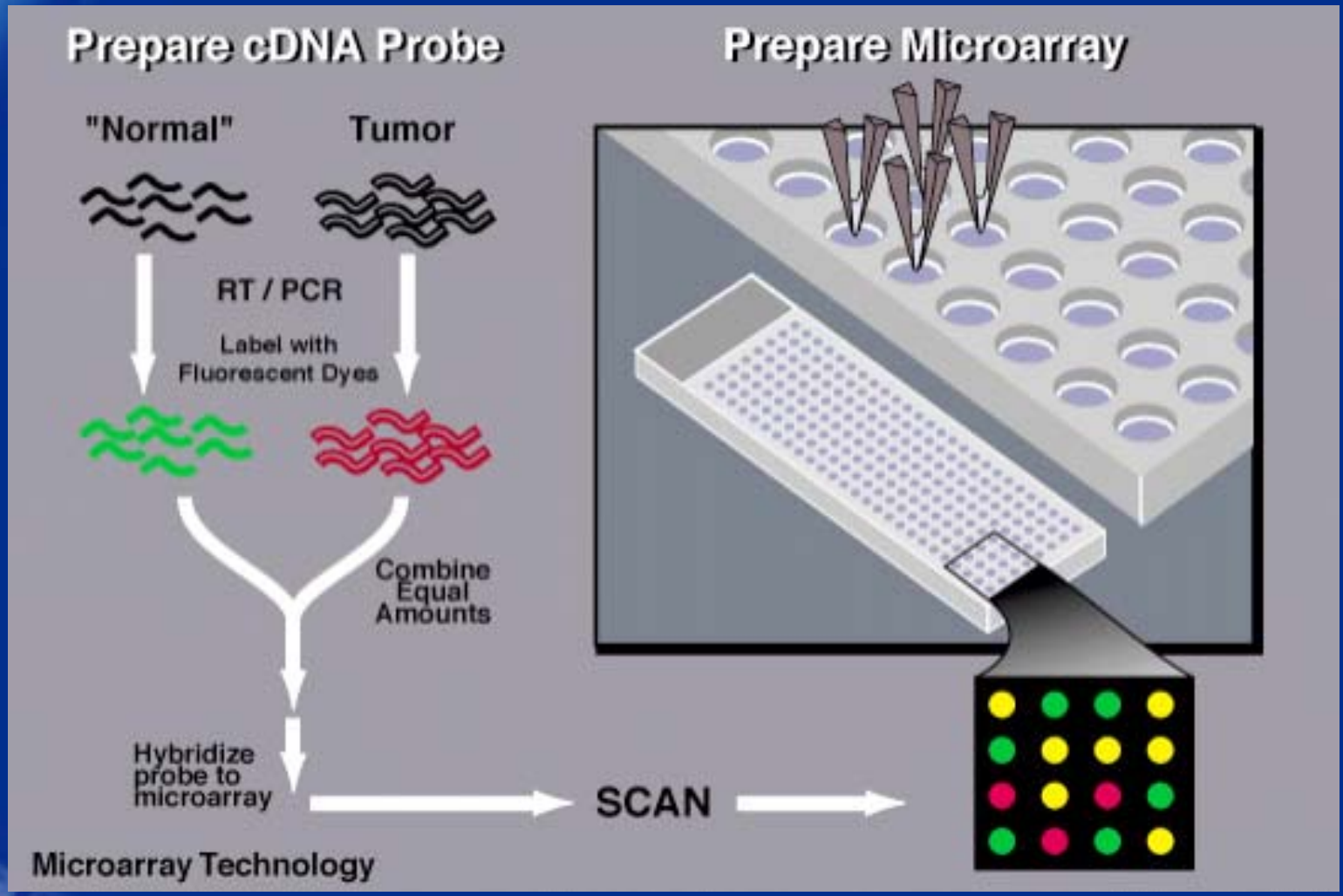
Tissue Multiple Array



Profil Protéomique sérique (PROTEIN CHIP, Ciphergen®™)

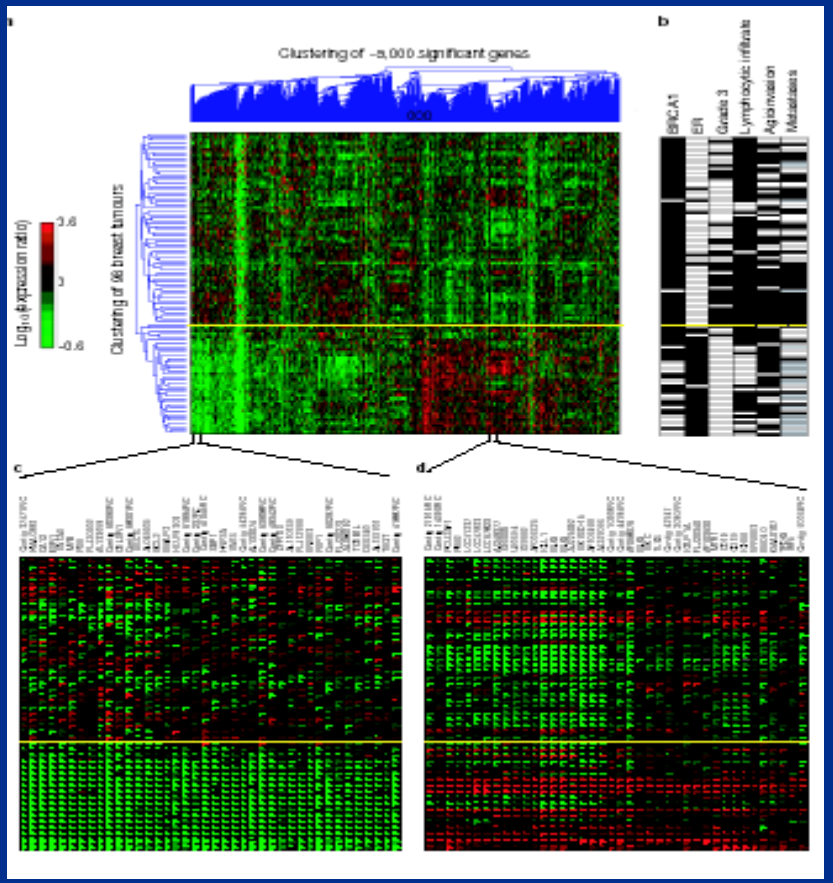


Puces à ADN


Prepare cDNA Probe
"Normal"
Tumor
RT / PCR
Label with
Fluorescent Dyes
Combine
Equal
Amounts
Hybridize
probe to
microarray
SCAN
Microarray Technology
Prepare Microarray

Gene expression profiling predicts clinical outcome of breast cancer

Laura J. van 't Veer*†, Hongyue Dai†‡, Marc J. van de Vijver*†, Yudong D. He‡, Augustinus A. M. Hart*, Mao Mao‡, Hans L. Peterse*, Karin van der Kooy*, Matthew J. Marton‡, Anke T. Witteveen*, George J. Schreiber‡, Ron M. Kerkhoven*, Chris Roberts‡, Peter S. Linsley‡, René Bernards* & Stephen H. Friend‡

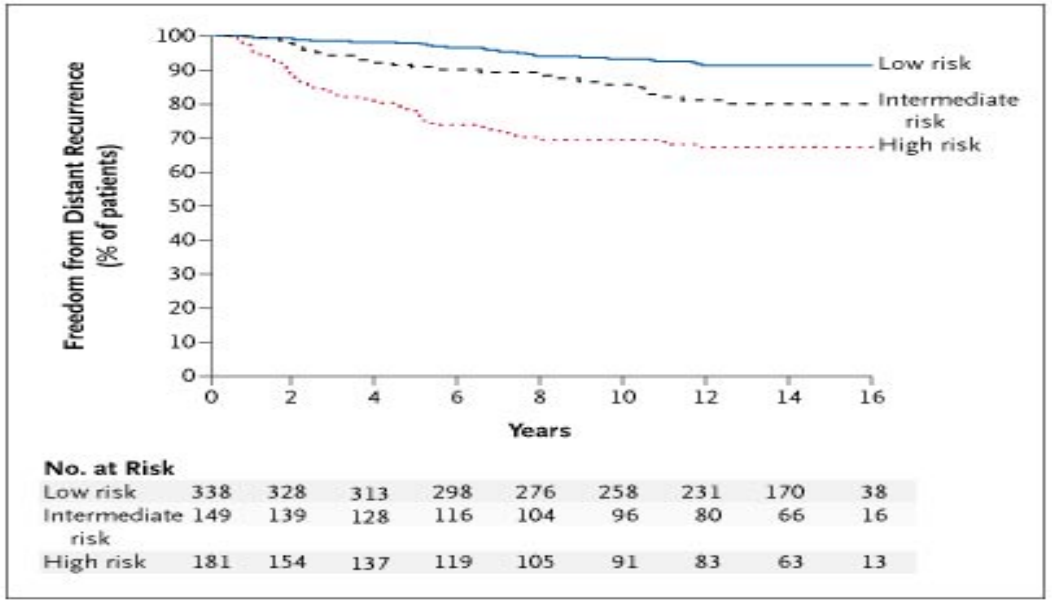


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Multigene Assay to Predict Recurrence of Tamoxifen-Treated, Node-Negative Breast Cancer

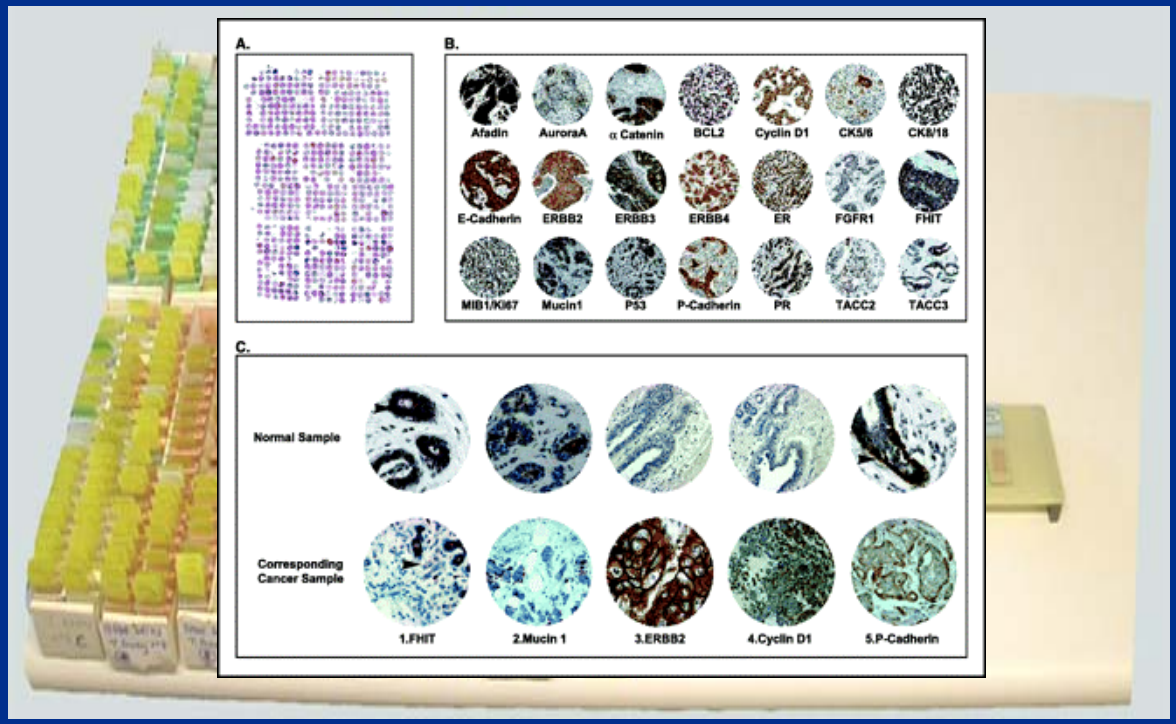
Soonmyung Paik, M.D., Steven Shak, M.D., Gong Tang, Ph.D., Chungyeul Kim, M.D., Joffre Baker, Ph.D., Maureen Cronin, Ph.D., Frederick L. Baehner, M.D., Michael G. Walker, Ph.D., Drew Watson, Ph.D., Taesung Park, Ph.D., William Hiller, H.T., Edwin R. Fisher, M.D., D. Lawrence Wickerham, M.D., John Bryant, Ph.D., and Norman Wolmark, M.D.



No. at Risk

Low risk	338	328	313	298	276	258	231	170	38
Intermediate risk	149	139	128	116	104	96	80	66	16
High risk	181	154	137	119	105	91	83	63	13

Expression of oncogene products and tumor suppressors in breast cancers

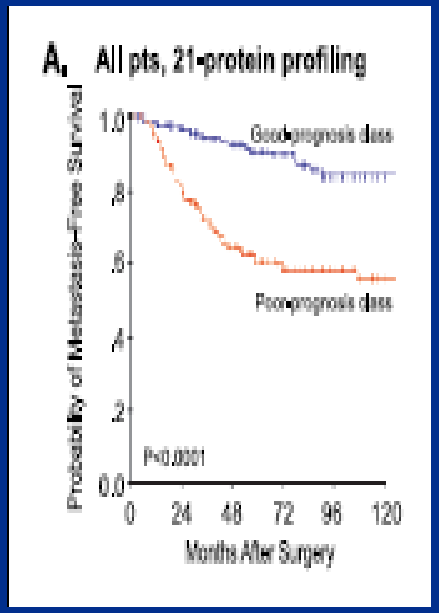


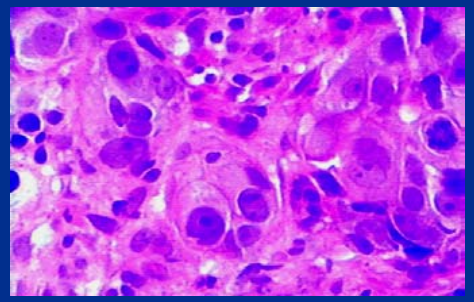
Tissue Multiple Array

Protein Expression Profiling Identifies Subclasses of Breast Cancer and Predicts Prognosis

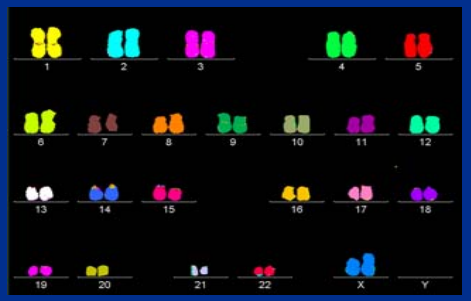
Jocelyne Jacquemier,[1,2] Christophe Ginestier,[1] Jacques Rougemont,[6] Valérie-Jeanne Bardou,[3] Emmanuelle Charafe-Jauffret,[1,2,7] Jeannine Geneix,[1] José Adélaïde,[1] Alane Koki,[6] Gilles Houvenaeghel,[4] Jacques Hassoun,[3,7] Dominique Maraninchi,[5,7] Patrice Viens,[5,7] Daniel Birnbaum,[1] and François Bertucci[1,5,7]

[1]Institut de Cancérologie de Marseille, Département d'Oncologie Moléculaire, [2]BioPathologie, [3]BioStatistiques, [4]Chirurgie, and [5]Oncologie Médicale et Investigation Clinique, Institut Paoli-Calmettes and UMR599 Institut National de la Santé et de la Recherche Médicale; [7]ERM206 Institut National de la Santé et de la Recherche Médicale; [7]Université de la Méditerranée, UFR de Médecine; and [6]Ipsogen S.A., Marseille, France

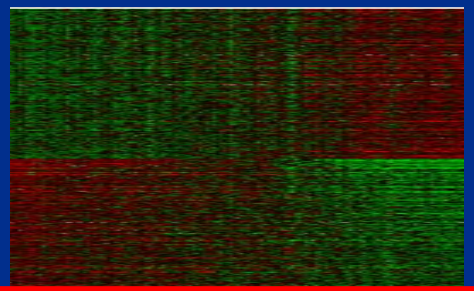




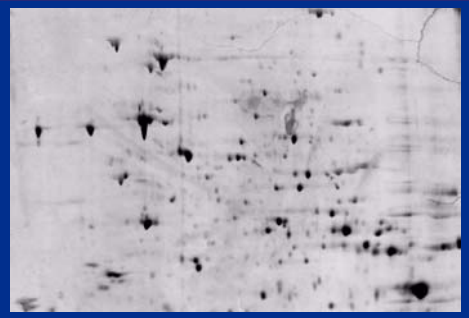
Morphologie



Chromosomes



Gènes

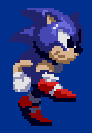


Protéines

Protein ID

Before

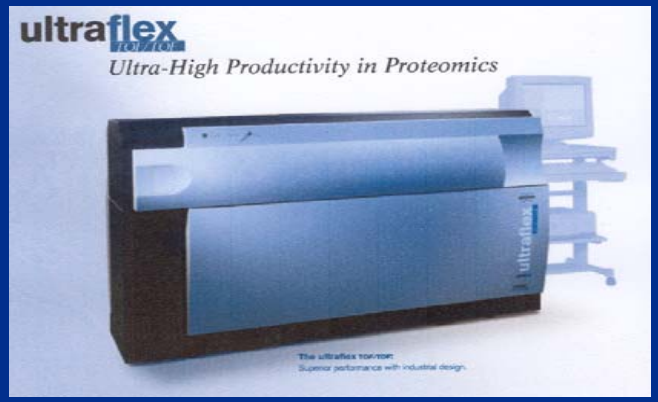
Now

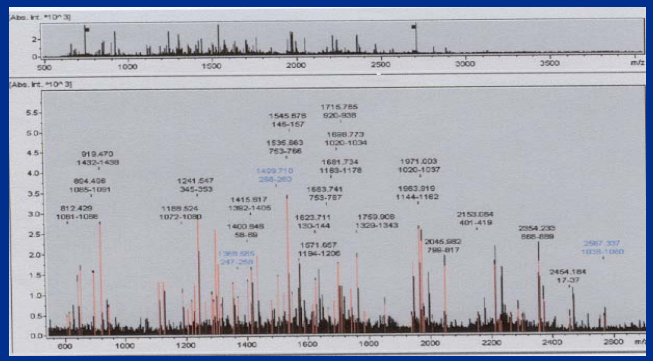


MALDI-TOF analysis

Peptide mapping

Identification





Nominal mass of protein (M_r): 164520
Fixed modifications: Carbamidomethyl (C)
Cleavage by Trypsin: cuts C-term side of KR unless next residue is P
Sequence Coverage: 23%
NCBI BLAST search of SYHUQT against nr
Calculated pI value: 7.77
Unformatted sequence string for pasting into other applications

Matched peptides shown in Bold Red

```
   1 MEETKIDHWL EFSATKLSSC DSFTSTINEL NHCLSLRTYL VGNELSLADL
  51 CVGATLKGNA AWQEQLKQKK APVHVERWFG FLEAQQAFQS VGTKWDVSTT
 101 KARVAPEKKQ DVGKFVELFG AEMGEVTVRF PPEASGTLHI GHAKAALLNQ
 151 HYQVHFKGKL IMRFDDTNPE KEKEDFEKVI LEDVAMLHIK PDQFTYTSDH
 201 FETIMKYAEK LIQEGKAYVD DTPAEQMKAE REQRIESKHR KNPIEKNLQN
 251 WEEMKKGSQF GHSCCLRAKI DMSSHNGCHR DPTLYRCKIQ PHPRTGNKYN
 301 VYPTYDFACP IVDSIEGVTH ALRTTEYHDR DEQFYWIIEA LGIRKPYIWE
 351 YSRLNLNNTV LSKRKLTDFV NEGLVDGWDD PRFFTVRGVL RRGMTVEGLR
 401 QFIAAQGSSR SVVHHDWDKI WAFNKEVIDP VAPRYVALLK KEVIPVNVPE
 451 AGEEMKEVAK EPKNPEVGLK PVWYSPKVFI EGADAETFSE GEMVTFINWG
 501 NLNITKIHKN ADGKIISLDA KFNLENKDYK KTTKVTWLAE TTHALPIPVI
 551 CVTYEHLITK PVLGKDEDFK QYVNKNSKHE ELMLGDPCLK DLKKGDIIQL
 601 QRRGFFICDQ PYEPVSPYSC KEAPCVLIYI PDGHTKEMPT SGSKEKTKVE
 651 ATKNETSAPF KERPTPSLNN NCTTSEDSLV LYNRVAVQGD VVRELKAKKA
 701 PKEDVDAAVK QLLSLKAEYK EKTGQEYKPG NPPAEIGQNI SSNESASLLE
 751 SRSLYDEVAA QGEVVDKLRA EKSPKAKINE AVECLLSLKA QYKEKTGKTV
 801 IPGQPPLSQS SDSSPTPNSE PAGLETPEAK VLFDKVASQG EVVRKLKTEK
 851 APRDQVDIAV QELLQLKAQY KSLIGVEYKP VSATGAEDKD KKKKEKENKS
 901 EKQNKPQKQN DGQRKDPSKN QGGGLSSSGA GEGQGPKKQT RLGLKAKKEE
 951 NLADWYSQVI TKSENIEYHD ISGCYILRPW AYAIWEAIKD FFDAEIKKLG
1001 VENCYFPMFV SQSALEKEKT HVADFAPEVA WVTRSGKTEL AEPIAIRPTS
1051 ETVMYPAYAK WVQSHRDLPI KLNQWCHVVR WEFKPQPFL WTREFLWQEG
1101 HSAFATMEEA AEEVLQILDL YAQVYEELLA IPVVKGRKTE KEKFAGGDYT
1151 TTIEAFISAS GRAIQGGTSH HLGQHFSKKF EIVFEDPKIP GEKQFAYQNS
1201 WGLTTRTIGV MTMVHGDNRG LVLPPRVACV QVVIIPCGIT NALSEEDKEA
1251 LIAKCNDYRR RLLSVNIRVR ADLRDNYSPG WKFNHWELKG VPIRLEVGPR
1301 DMKSCQFVAV RRDTGEKLTV AENEAETKLQ AILEDIQVTL FTRASEDLKT
1351 HHVVANTNED FQKILDSGKI VQIPFCGEID CEDWIKKTTA RDQDLEPGAP
1401 SNGAKSLCIP FKPLCELQPG AKCVCGKNPA KCXTLFGRSY
```

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Jean-Paul Borg, Group leader

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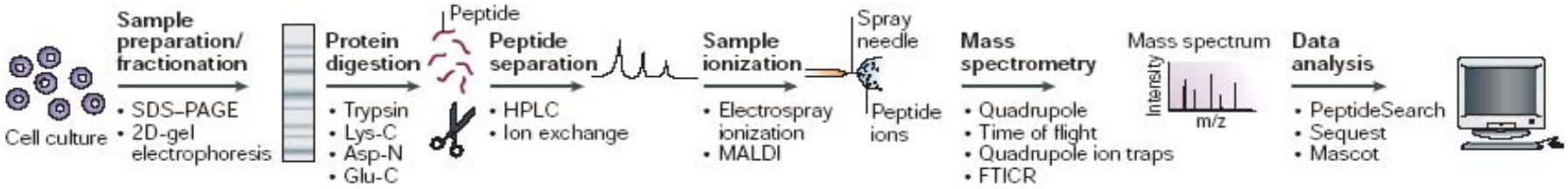
PROVENCE-ALPES-CÔTE D'AZUR

Protein identification: measurement of specific m/z ratios of peptides

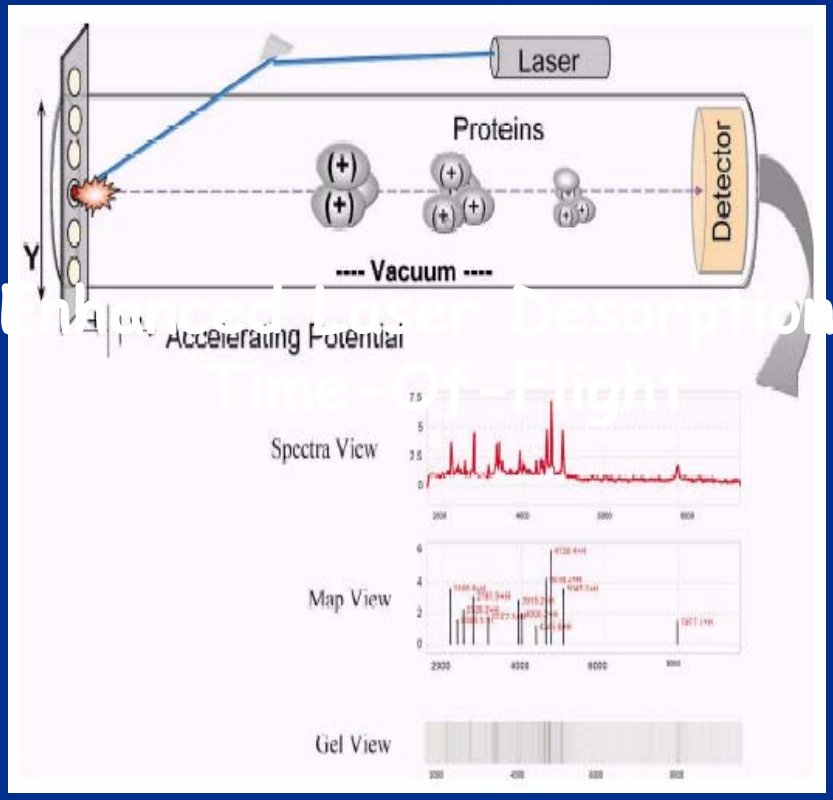


Obtention of peptides

Analysis

Identification

Looking for novel biomarkers in the serum using the SELDI-TOF technology

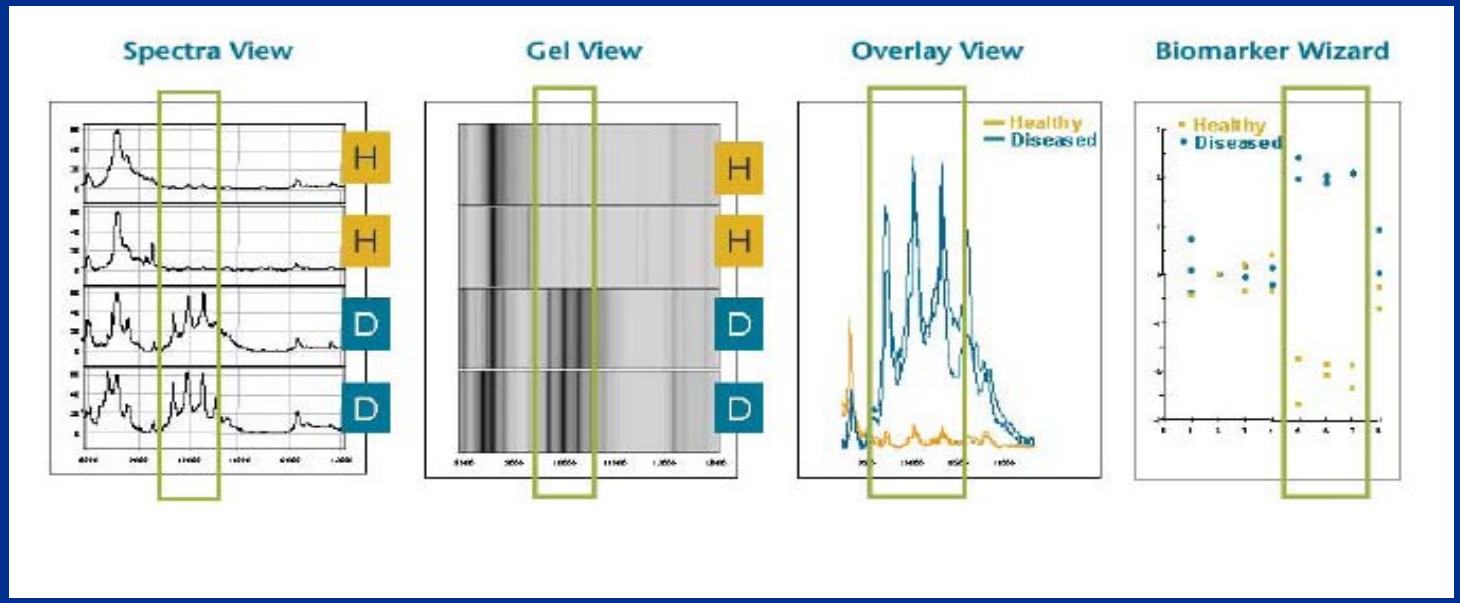


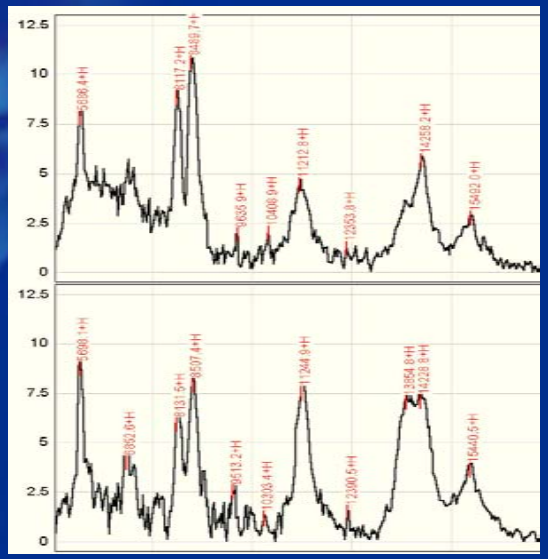
Surface Enhanced Laser Desorption Ionisation Time-Of-Flight

SELDI Protein Chips

- Hydrophobic (C_8) Arrays
- Hydrophilic (SiO_2) Arrays
- Anion exchange Arrays
- Cation exchange Arrays
- Immobilized Metal Affinity (NTA-nitroloacetic acid) Arrays
- Epoxy Surface (amine and thiol binding) Arrays

SELDI technology





Normal

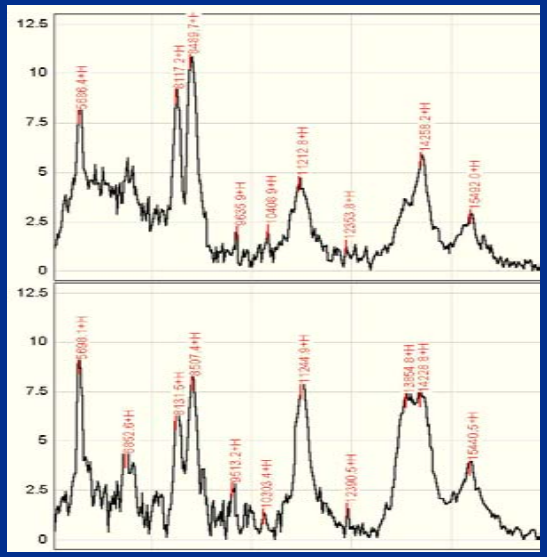
Tumor

Lancet 2002; **359:** 572–77

Use of proteomic patterns in serum to identify ovarian cancer

Emanuel F Petricoin III, Ali M Ardekani, Ben A Hitt, Peter J Levine, Vincent A Fusaro, Seth M Steinberg, Gordon B Mills, Charles Simone, David A Fishman, Elise C Kohn, Lance A Liotta

* Ovary cancer: a need for detection of early-stage ovarian cancer
* 5 years survival for patients at a late clinical stage is 35% vs 90% at stage I
* CA125 is abnormal in 80% of late clinical stage. This drops to 50% in stage I



Normal

Ovarian cancer

Early Breast Cancer

Lymph node invasion
ER/PR
Tumor size
SBR Grade
age

« Good risk »

<20% of metastatic relapse

« Poor risk »

Up to >50% of treatment failure

Serum Proteomics and prognosis of « poor-risk » Early Breast Cancer

81 Early Breast Cancer patients with poor-risk features (pN+ and/ or ER-; Grade III, Age <40, Tumor size > 20 mm)

Primary Tumor excision and lymph node dissection

All patients received adjuvant CT and HT if applicable

Serum post-operatively collected within 21 days after surgery

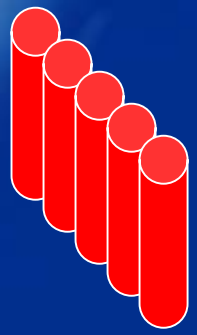
33 patients being disease-free after a minimum follow-up of 6 years and 48 with metastatic relapse within 6 years

Post-operative Serum protein Profile predicting for relapse ?

Patient Characteristics

N	81
Age	
median, range (Ys)	49 (27-78)
<40 (%)	14 (18%)
Lymph node invasion	
pN+ (%)	74 (91%)
Median number of LN, range	4 (0-26)
SBR Grade	
I/II	42 (52%)
III	37 (45%)
na	2 (3%)
Tumor size (mm)	
median, range	25(10-210)
Hormonal receptivity	
HR+	58 (71%)
HR-	20 (26%)
na	3 (3%)
Histologic type	
Ductal	63 (78%)
Lobular	9 (11%)
other	9 (11%)

Serum Protein Profiling



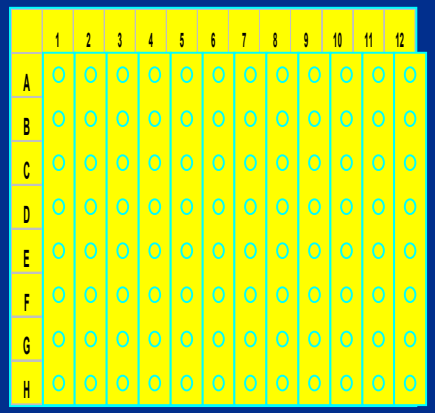
Serum Samples

F1

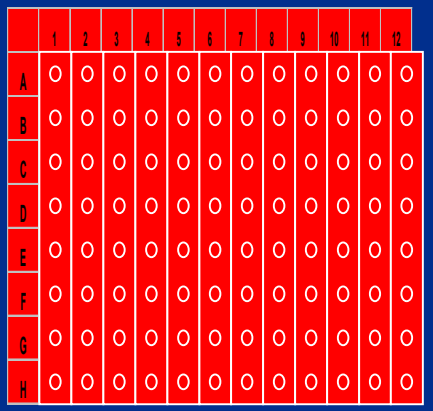
F4

F6

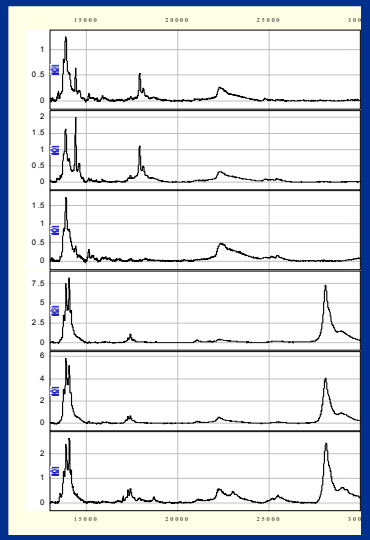
Fractionation using chromatographic anion exchange beads



CM10 (Cation exchange) ProteinChip arrays



IMAC30 (Cu++) ProteinChip arrays



Mass spectrometry

Y'en a un qui a tiré la langue pour faire tout ça, hein Anthony?

Sorry, I don't speak english (yet)!!

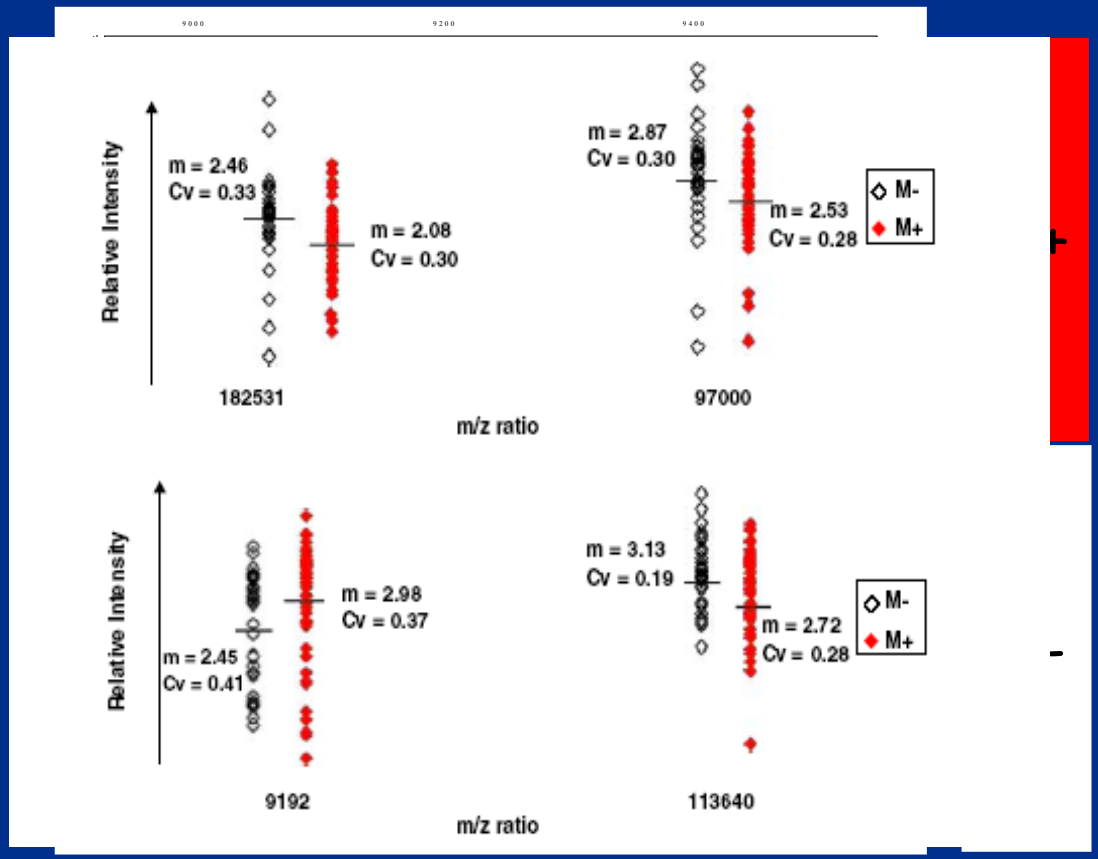
Some robotics is of great help!!

Modul-Bio
High-throughput solutions

Jeanne

Thanks Patrick, Jérome & ModulBio!!

Differentially expressed proteins according to the long term outcome (Metastatic vs Metastasis-free patients)

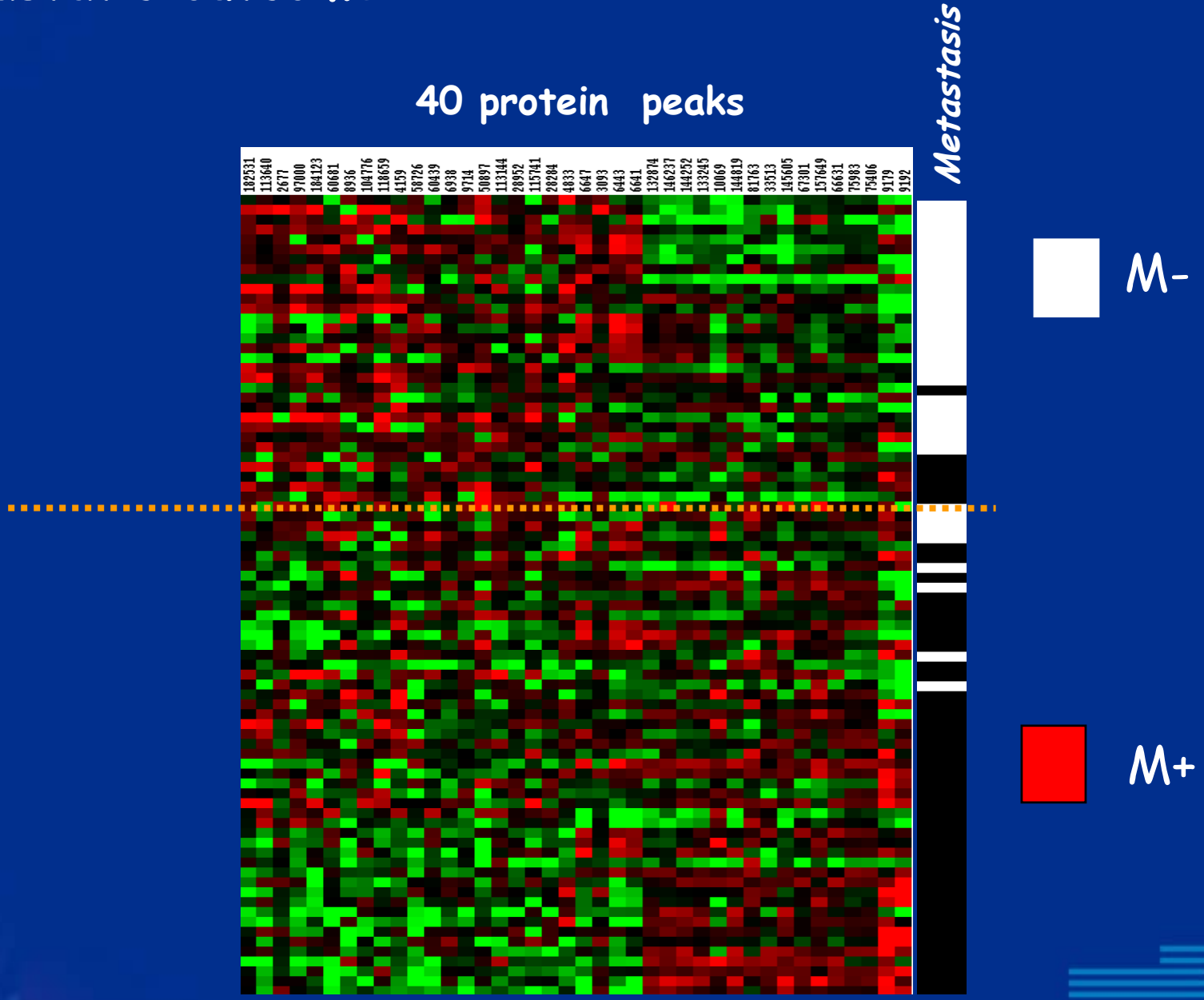


Upregulation of a protein with m/z ratio 9192 in early post-operative serum correlates with metastatic relapse

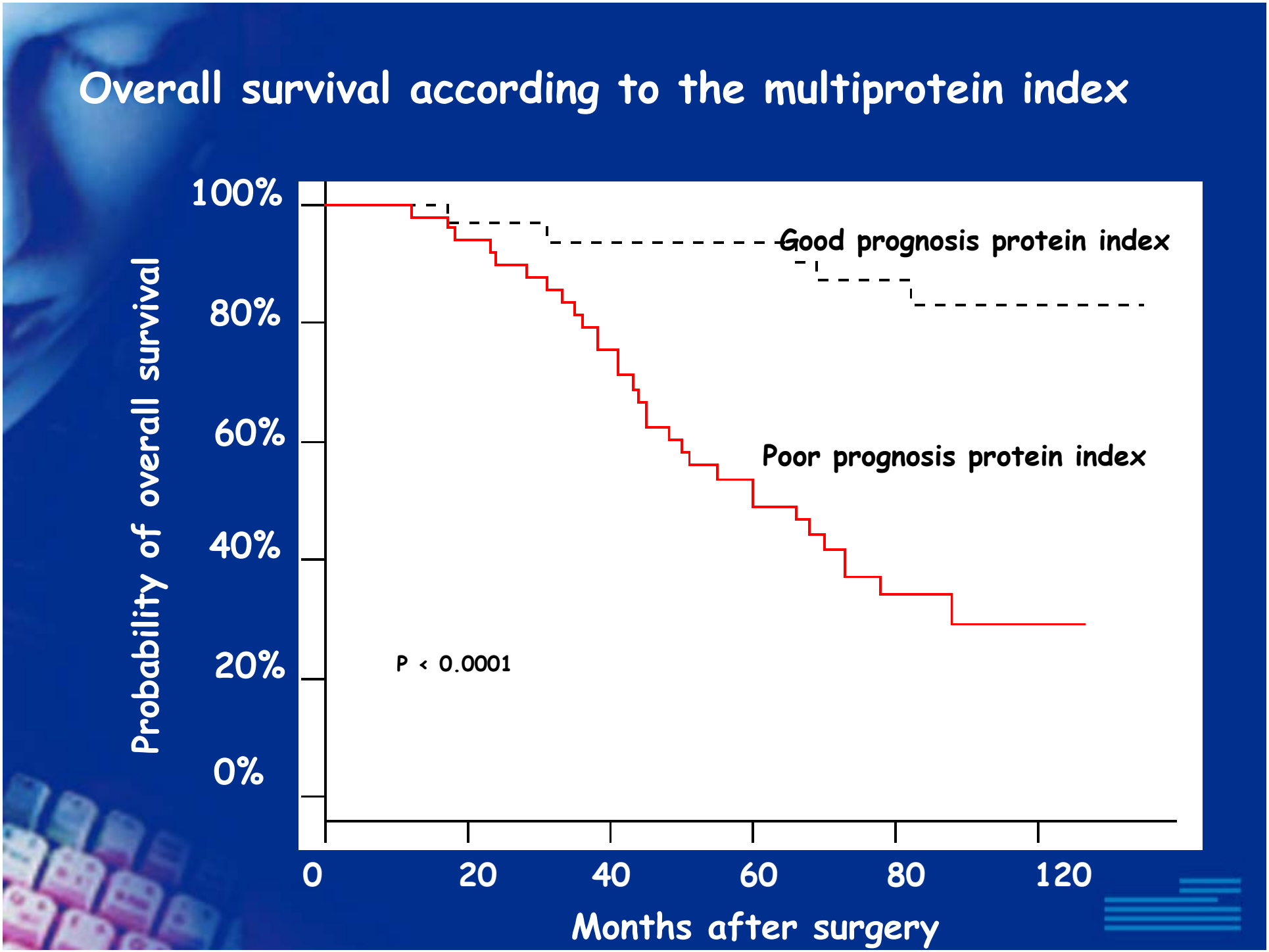
40 differentially expressed proteins according to the long term outcome (Metastatic vs Metastasis-free patients)

Experimental conditions (Fraction, ProteinChips)	Differentially expressed proteins (Ratio *m/z*) *(p <0.05, Mann Whitney test)*
F1 CM10	**2677 3093 8936 10069 113144**
F1 IMAC	**97000 104776 113640 115741 118659 182531 184123**
F4 CM10	**6938 9179 58726**
F4 IMAC	**4833 81763**
F6 CM10	**4159 6443 6641 6647 9714 28284 28952 33513 66631 67301 75406 75983 133245 144252 144819**
F6 IMAC	**9192 50897 60439 60681 132874 145605 146237 157649**

A signature of 40 protein peaks correlating with metastatic outcome



Overall survival according to the multiprotein index



Further studies are required

- To identify the proteins participating to the index

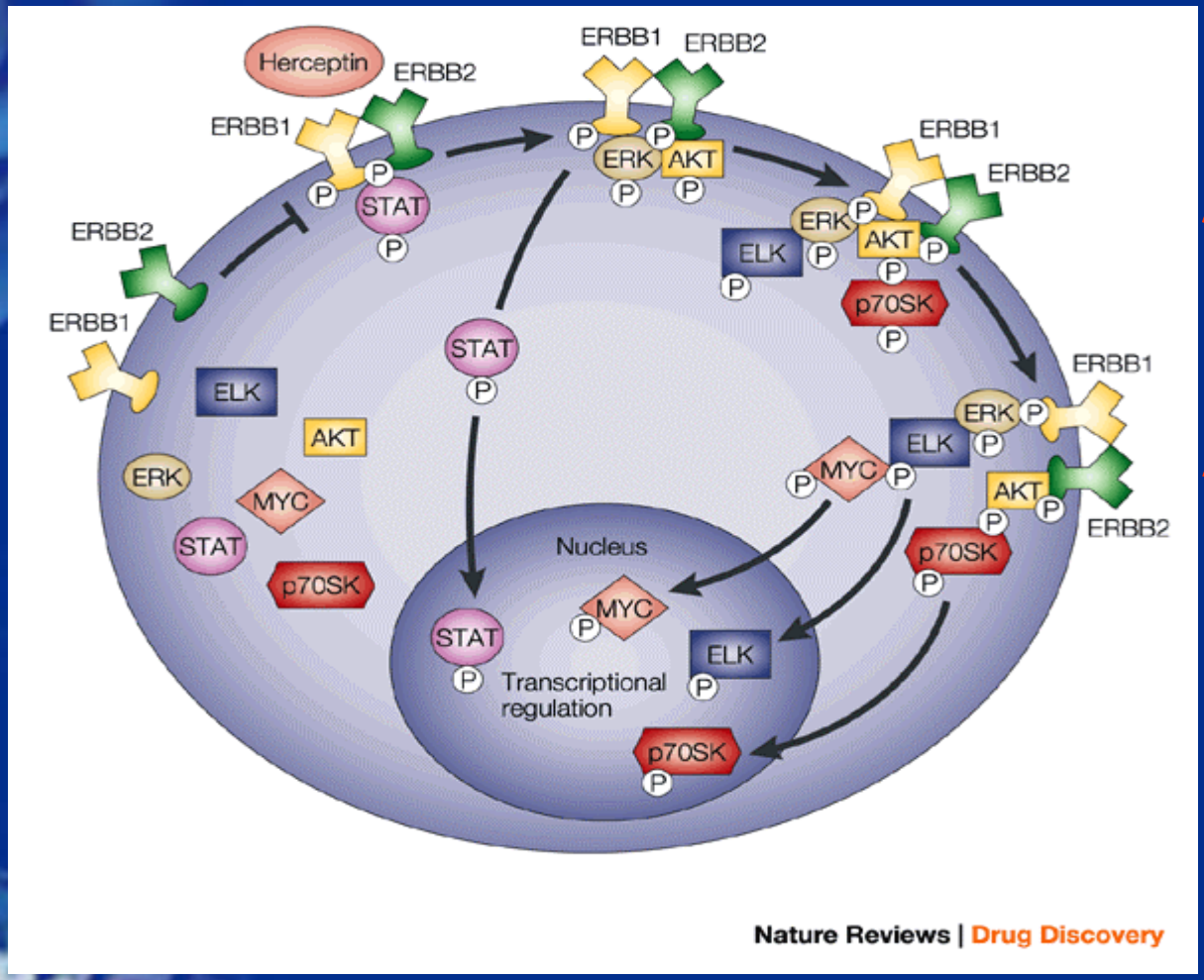
  Host response proteins with potential involvement in processes with critical role in the metastasis phenomenon (angiogenesis, immune response)

- Prospective collection for independent validation

TARGETED THERAPY

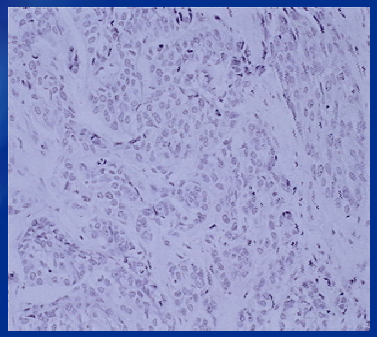
Nature Reviews Cancer
May 2004

HER2 in breast cancers



- Overexpressed in 30% of breast cancers
- Bad prognosis
- Trastuzumab: a mAb able to decrease oncogenicity

Metastatic breast cancers



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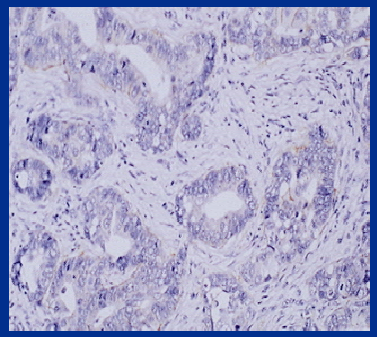
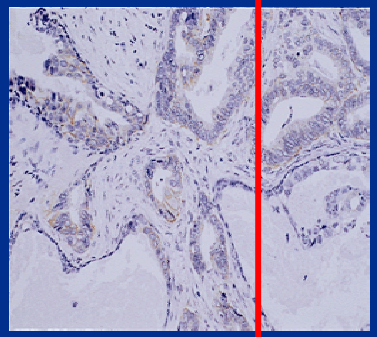
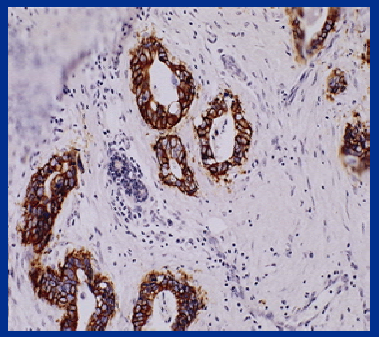


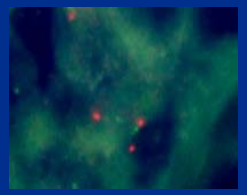
1+



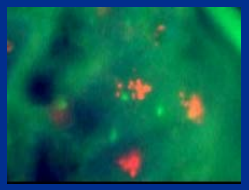
2+



3+



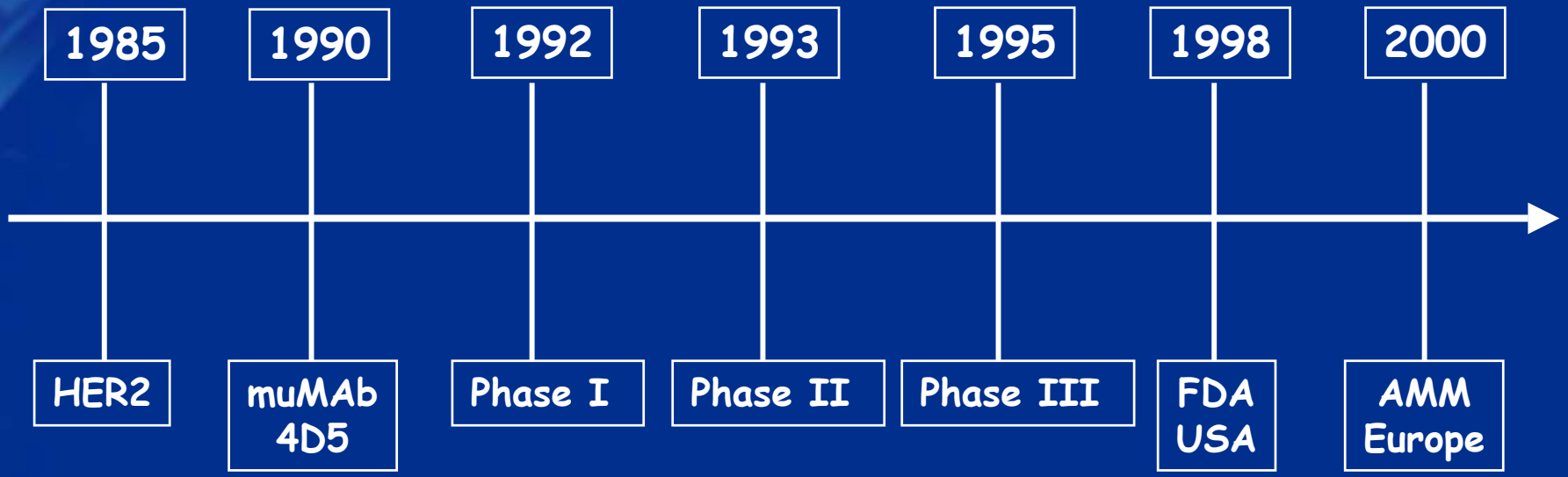
FISH -

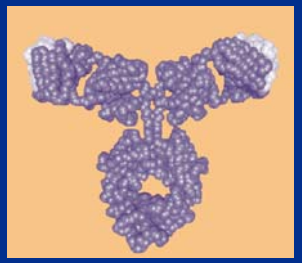


FISH +

combination trastuzumab + paclitaxel

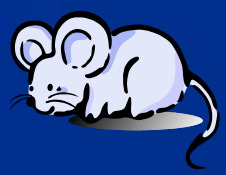
Herceptin: from the bench to the bedside

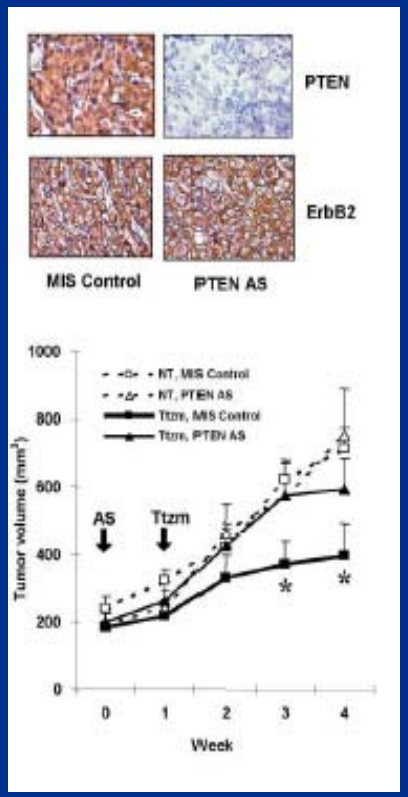


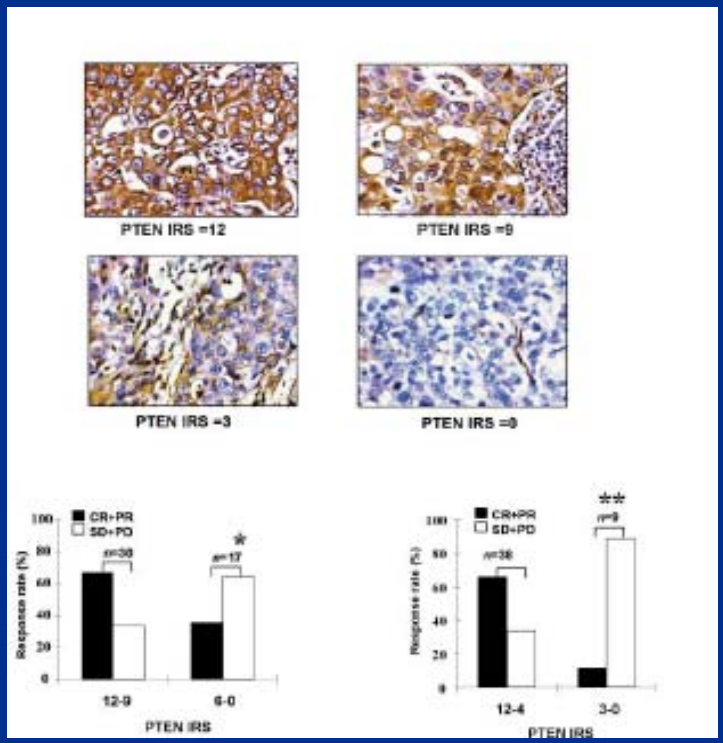



Cardiotoxicity
Resistance to the treatment

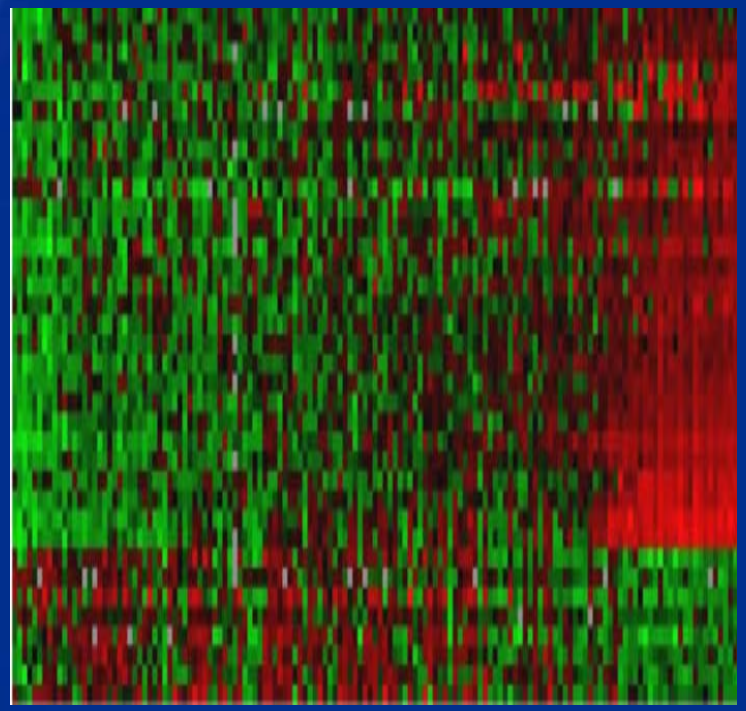
Tumors with PTEN deficiency have a poor response to Trastuzumab-based therapy



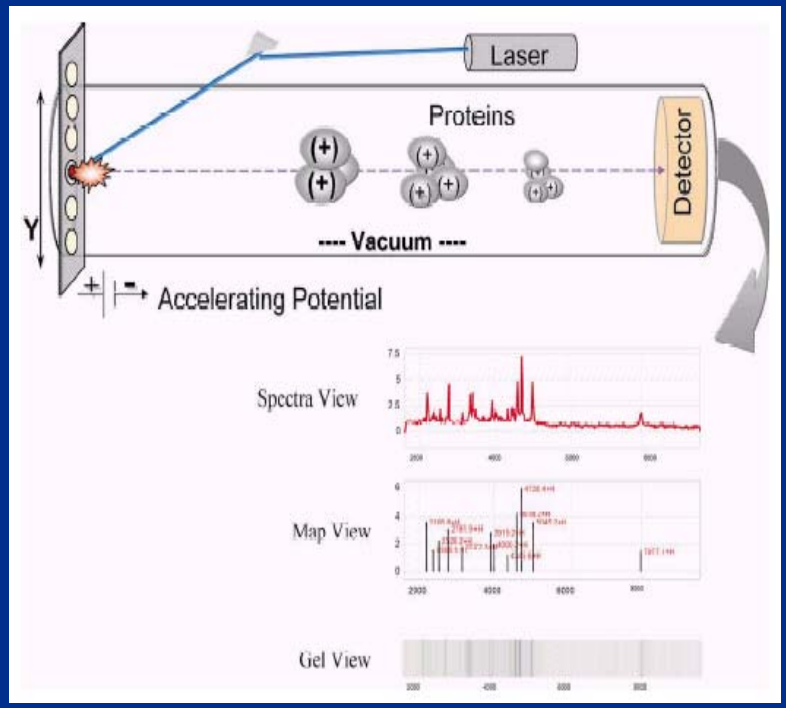




Toward the identification of an ERBB2 gene or protein signature to predict response to trastuzumab

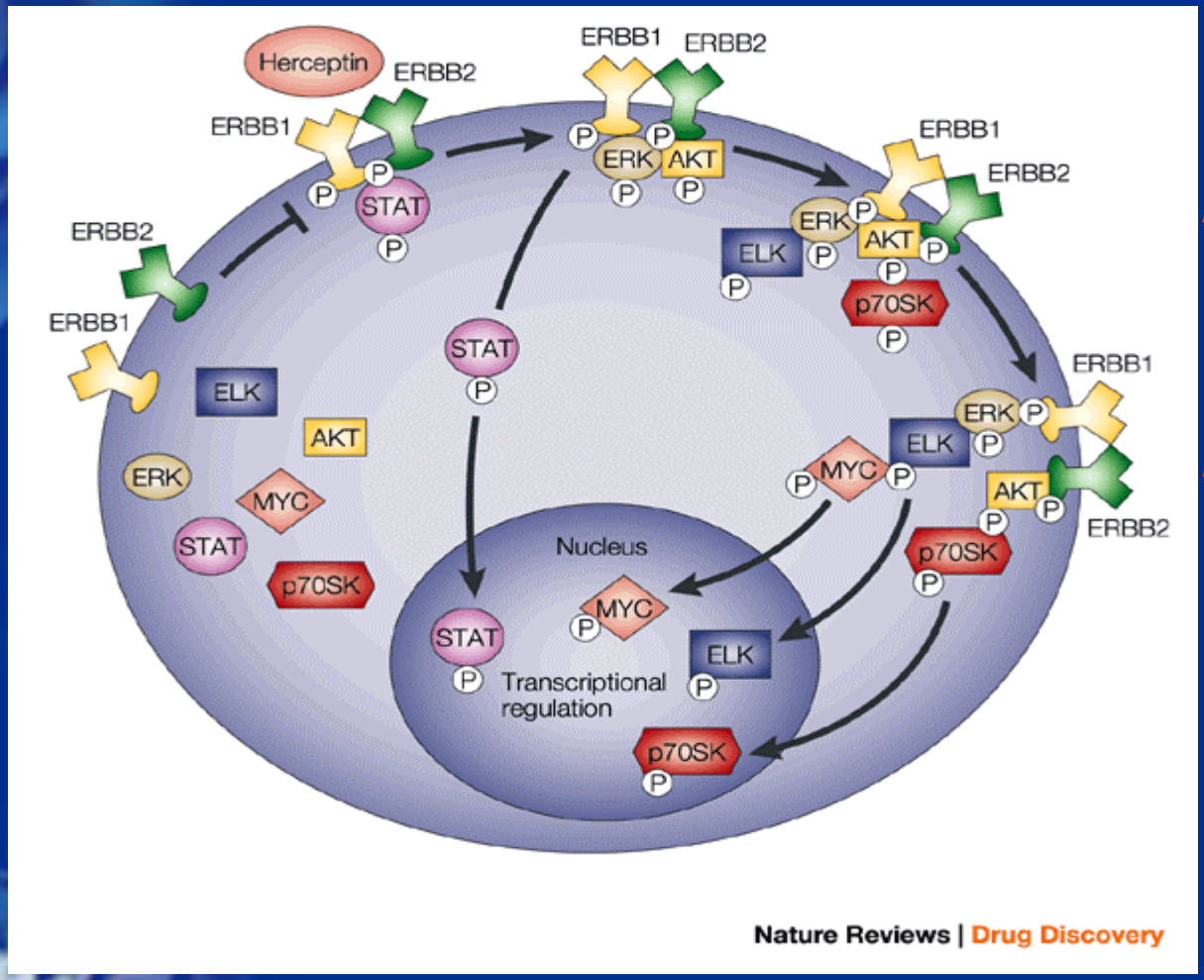


Tumor



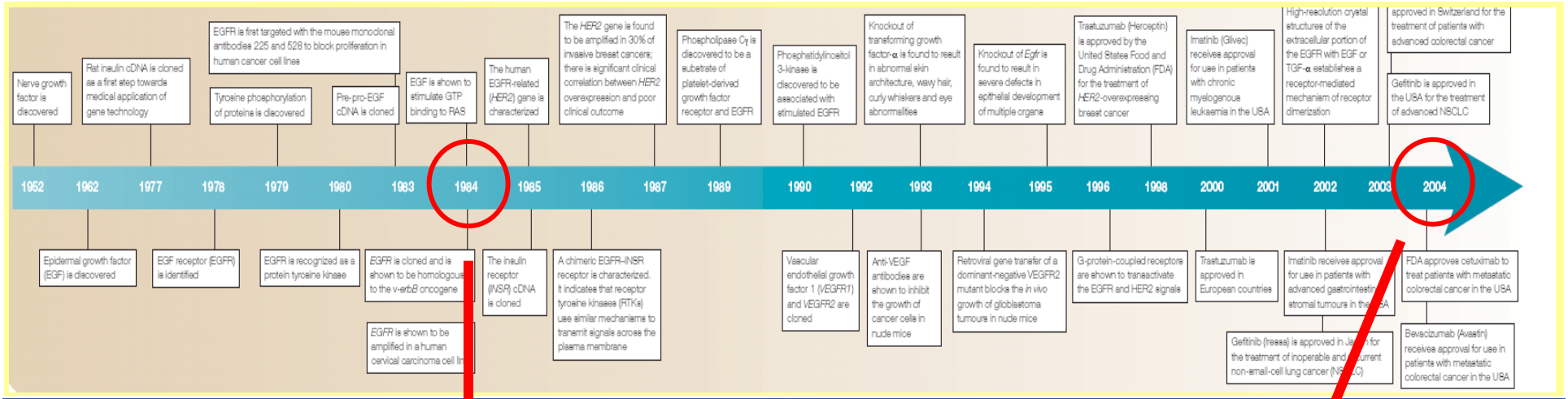
Tumor and/or serum

EGFR/ERBB1 in cancers



- Overexpressed or deregulated in many cancers
- Bad prognosis
- gefitinib: a TK inhibitor able to decrease oncogenicity

Twenty years: from the cloning of *egfr* to anti-Tyrosine Kinase therapies



1984: cloning of *egfr*

2004: a handful of anti-RTK drugs

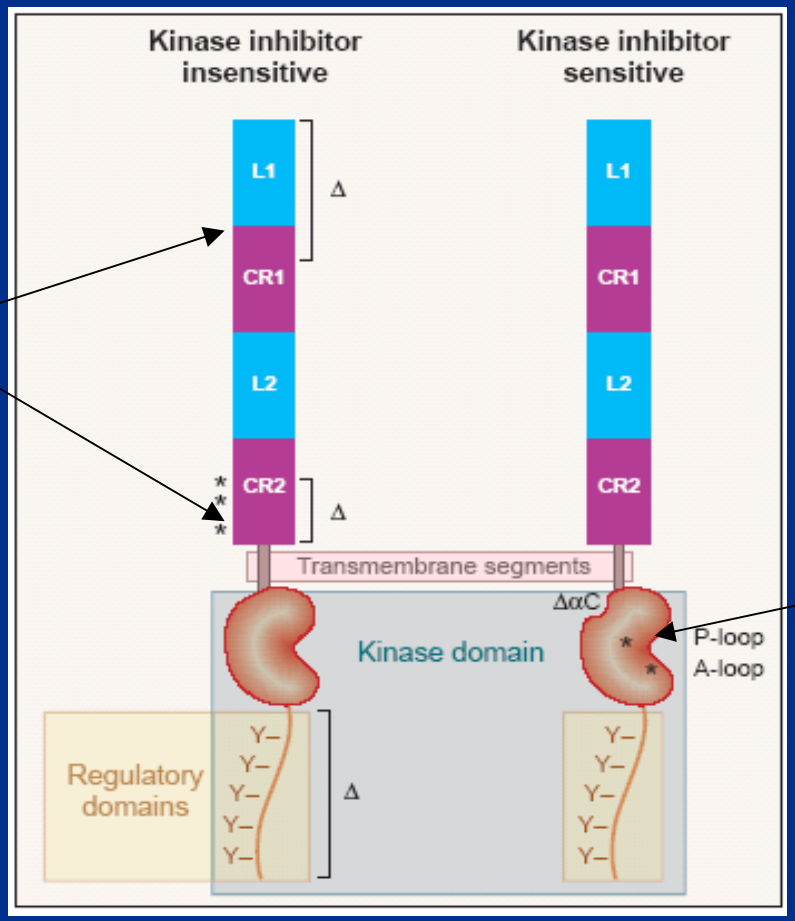
Nature Reviews Cancer
May 2004

Specificity of gefitinib

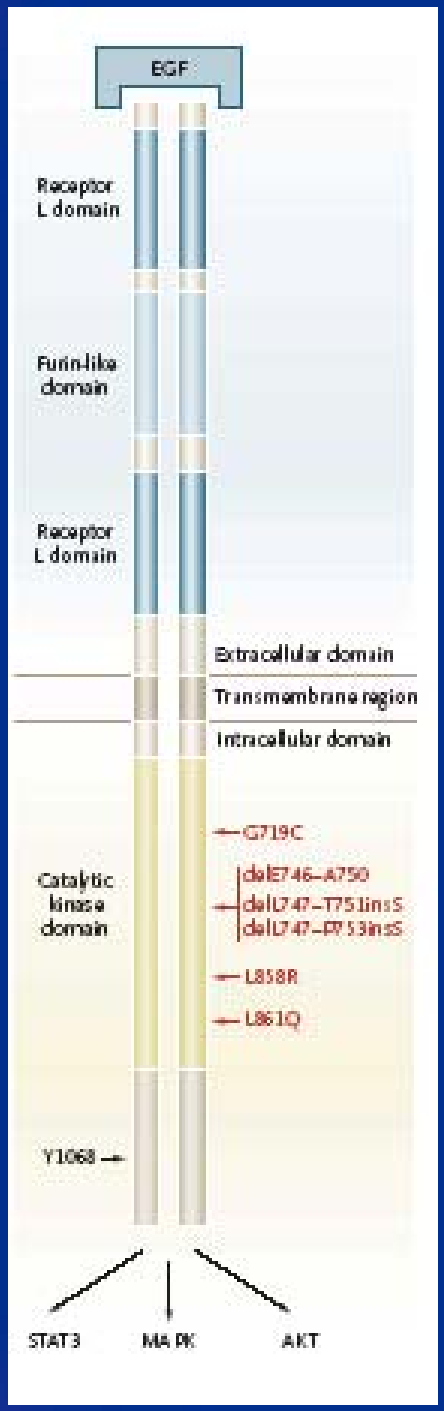
IC_{50} EGFR	0,033 μM
IC_{50} HER2	> 3,7 μM
IC_{50} VEGFR1	> 3,7 μM
IC_{50} VEGFR2	> 100 μM

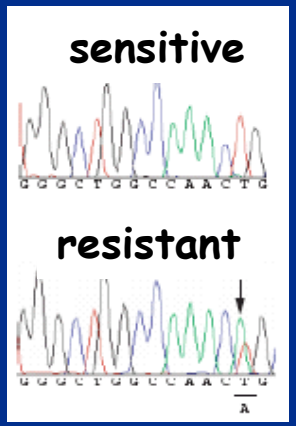
EGFR mutations in tumors that are sensitive or insensitive to kinase inhibitors

Glioblastomas



Lung cancers


EGF
Receptor L domain
Furin-like domain
Receptor L domain
Extracellular domain
Transmembrane region
Intracellular domain
Catalytic kinase domain
G719C
delE746–A750
delL747–T751insS
delL747–P753insS
L858R
L861Q
Y1068
STAT3
MAPK
AKT


sensitive
resistant

TARGETED THERAPY

Nature Reviews Cancer
May 2004


How to find new treatments ?

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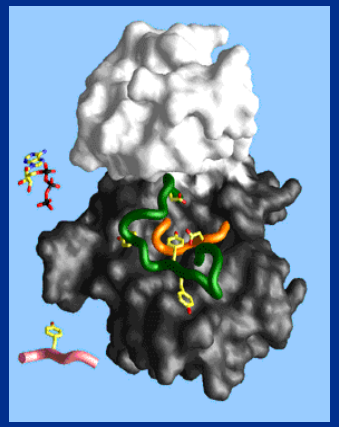
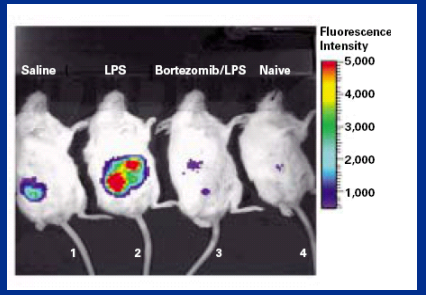
PAOLI-CALMETTES
PROVENCE-ALPES-CÔTE D'AZUR

protéine

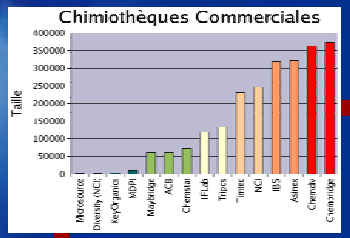


cible

médicament



Chimiothèques diverses.

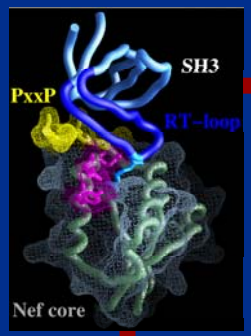


Filtrage

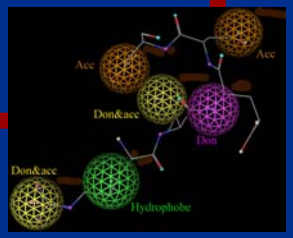
Chimiothèque Projet

Crible in silico

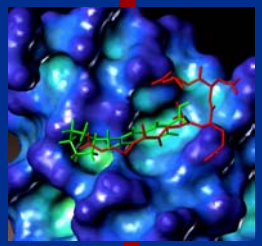
Cible Structure 3 D.



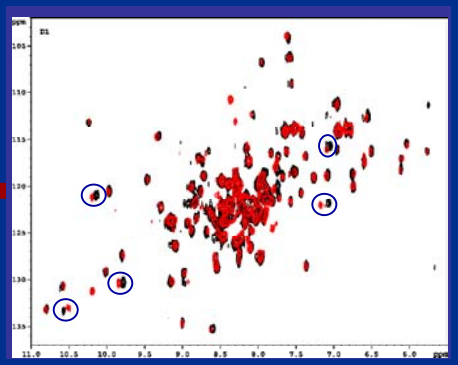
Pharmacophore.



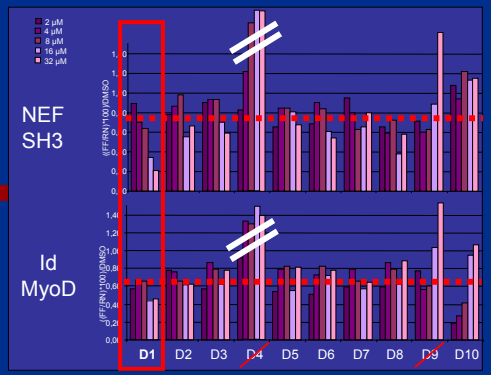
Liste de touches



Consolidation



Cribles expérimentaux



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MBio-LIMS™ - MODULE DE CRIBLAGE DE COMPOSES CHIMIQUES

Sauvegarde des données.

SERVEUR D'APPLICATION
SERVEUR DE BANQUE DE DONNEES
MBio-LIMS™

IMPRIMANTE CODE A BARRES ZEBRA

LUMINOMETRE BERTHOLD

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ROBOT DE PIPETAGE Aquarius, TECAN

Connaissance de l'identité des échantillons.
Communication des instruments entre eux.
Transmission automatique des données.

Interfaces Intranet accès sécurisé
(accès et analyse des données, validation des résultats, génération de rapports, etc.
import et export de données)

Microplaques pour composés chimiques

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Constance Brignatz, Thèse Immunologie
Audrey Restouin, tech IPC

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Pr P. Viens

BIoBank
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Dr R Sauvan

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Ciphergen
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