Cagliari 2010

"*L'oncologia medica molecolare: una nuova disciplina*

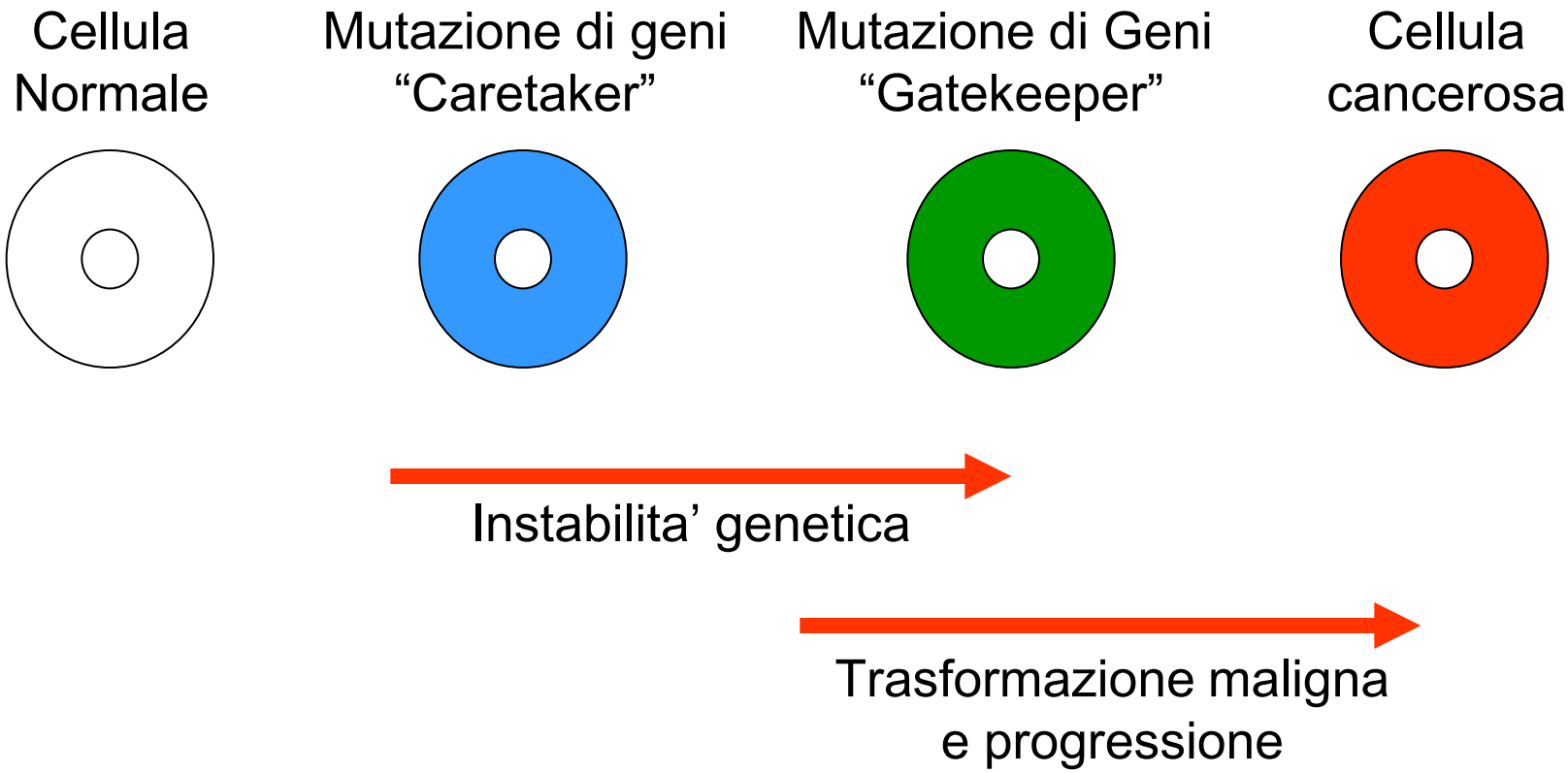
Paolo M Comoglio

Direttore Scientifico dell'
Istituto Per la Ricerca e la Cura del Cancro (IRCC-Candiolo)

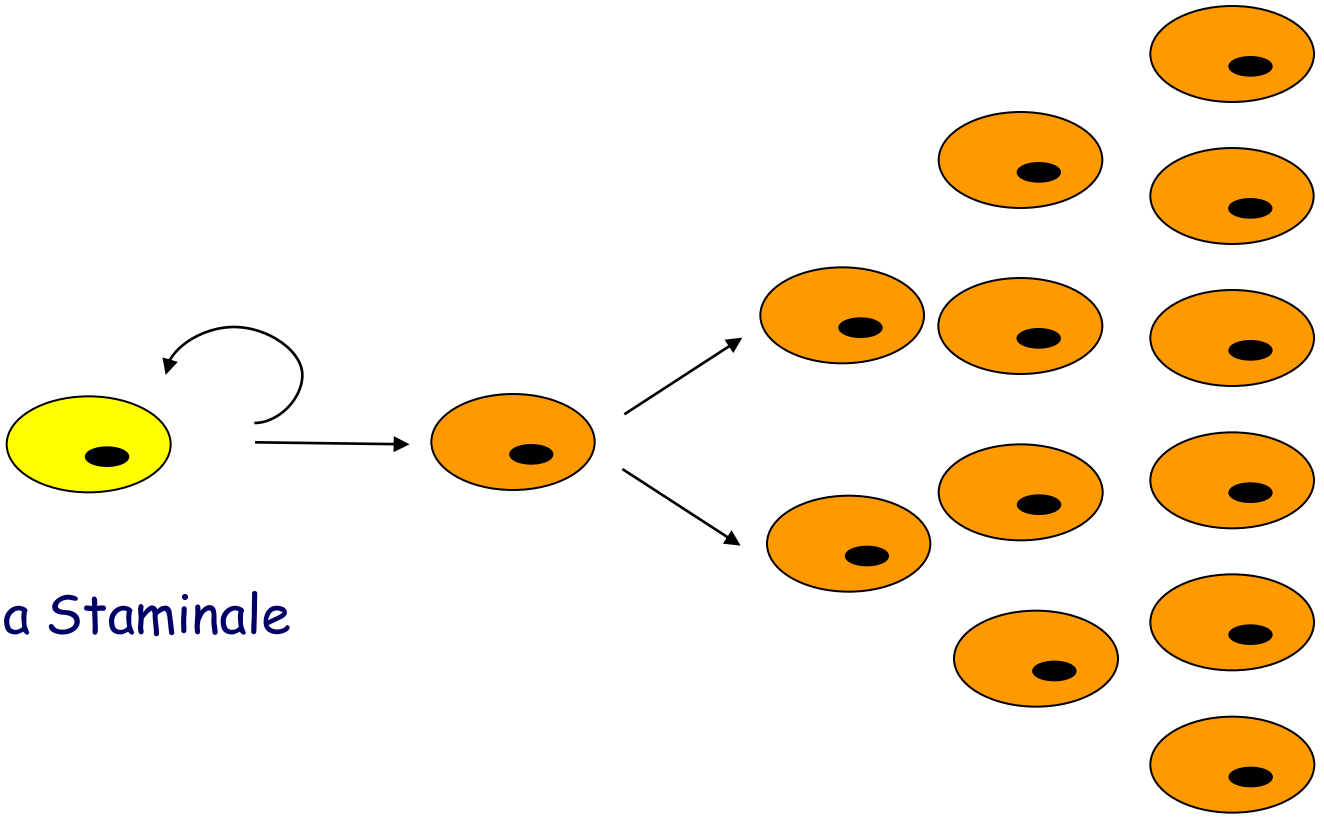
La Ricerca sul Cancro a un giro di boa

1. Il cancro e' una malattia genetica somatica
2. Origina (*probabilmente*) dalle cellule staminali
3. E' causato dalla mutazione di una manciata di geni
4. La diagnosi puo' identificare quali di questi geni sono mutati : Oncologia Molecolare
5. La terapia deve essere (*sara*') indirizzata contro i geni mutati : "Target Therapy"

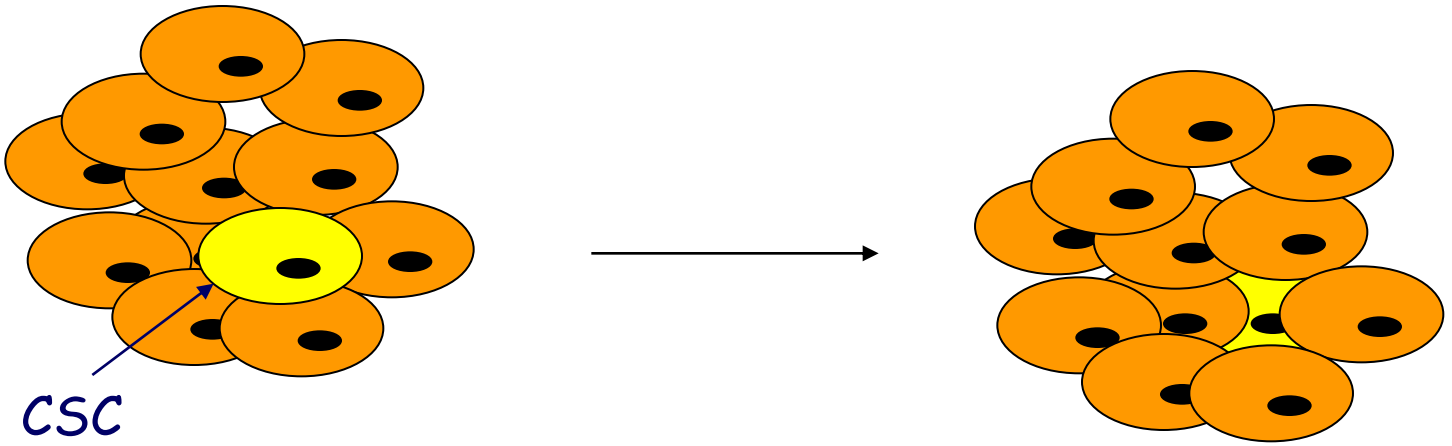
1 - Il cancro e' una malattia genetica *Somatica*



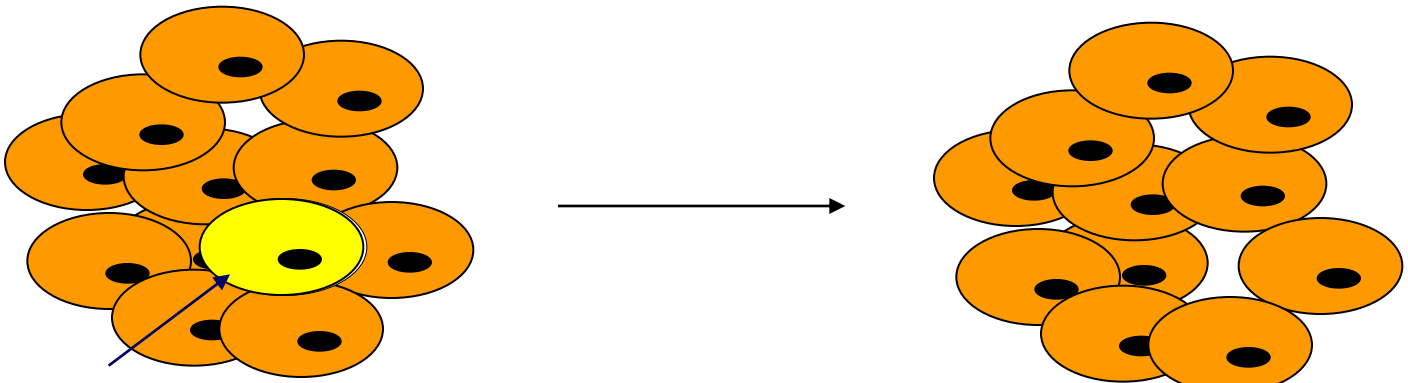
2 - Origina verosimilmente dalle *cellule staminali*



Le cellule staminali del cancro sono responsabili della ricaduta

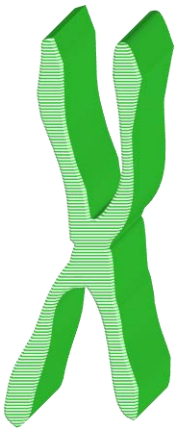


Le cellule staminali del cancro sono responsabili della ricaduta

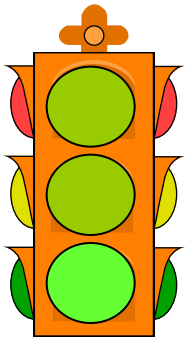


CSC

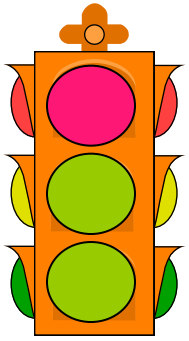
3 – Il Cancro e' causato dalla *mutazione* di una manciata di geni



Protooncogeni



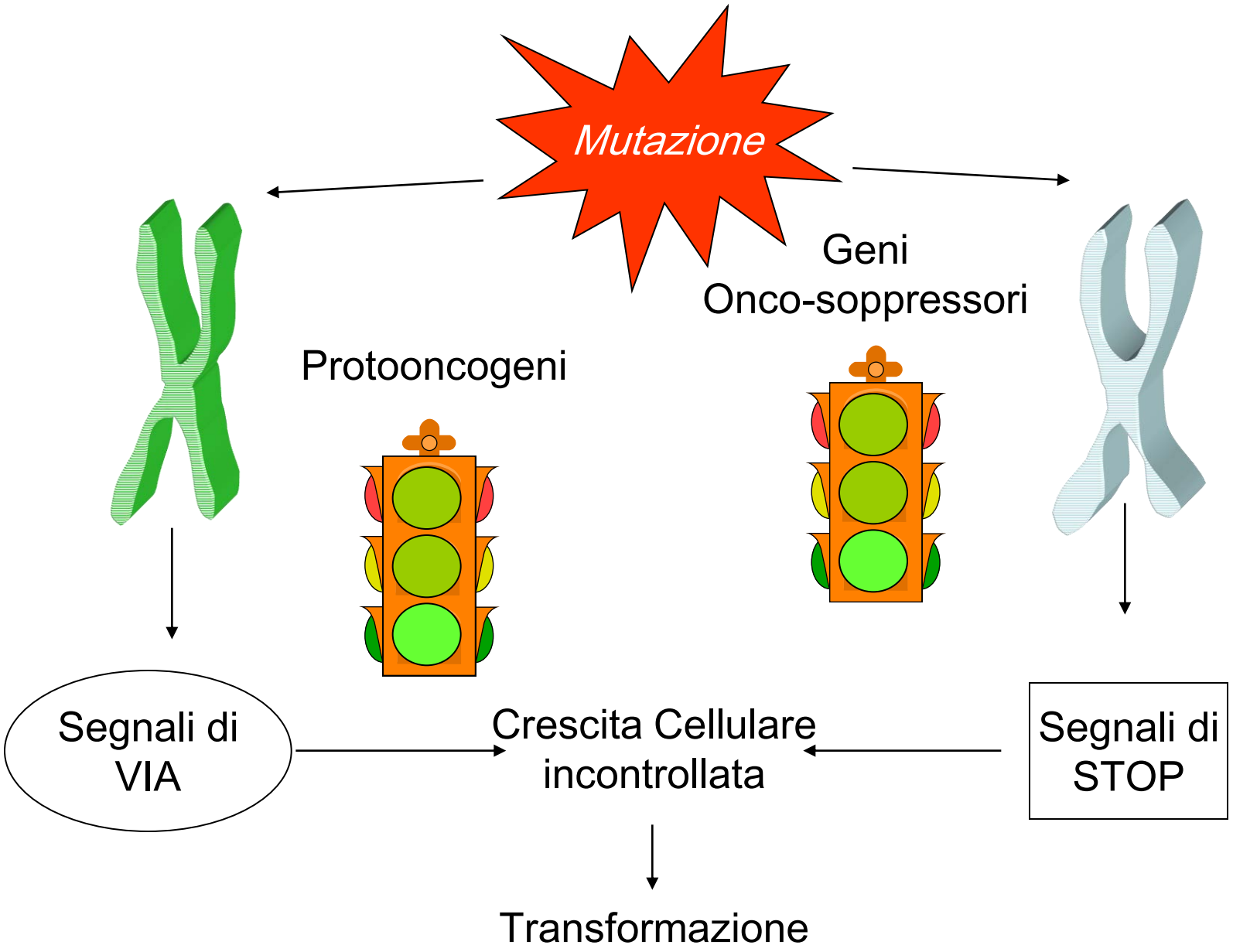
Geni
Onco-soppressori



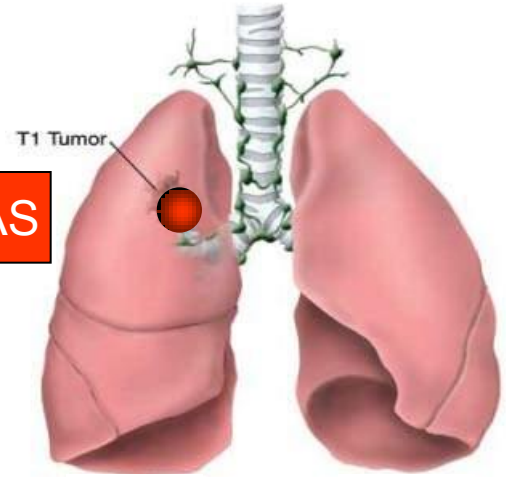
Segnali di VIA

Crescita Cellulare Controllata

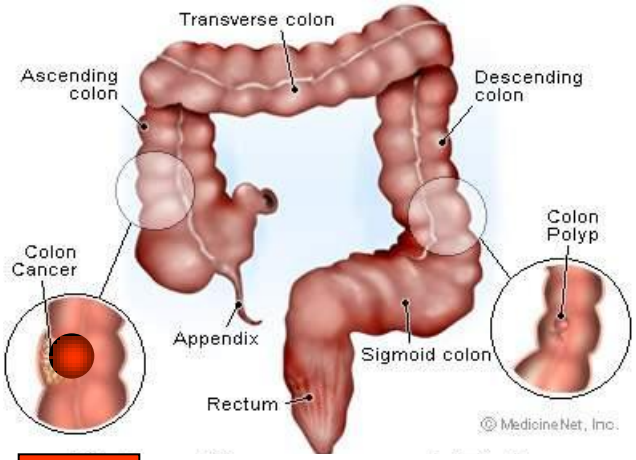
Segnali di STOP


Mutazione
Geni
Onco-soppressori
Protooncogeni
Segnali di
VIA
Crescita Cellulare
incontrollata
Segnali di
STOP
Transformazione

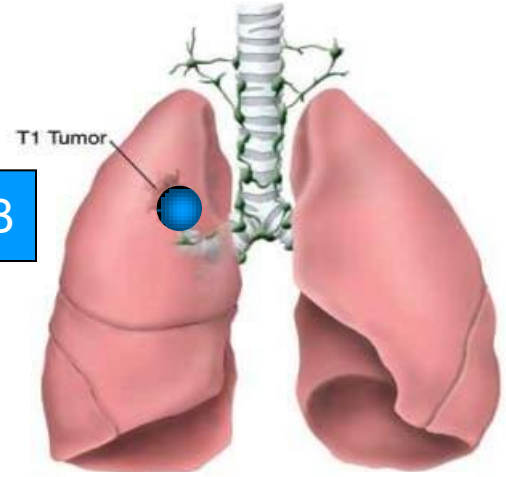
4 – La diagnosi molecolare identifica i geni responsabili della malattia



RAS



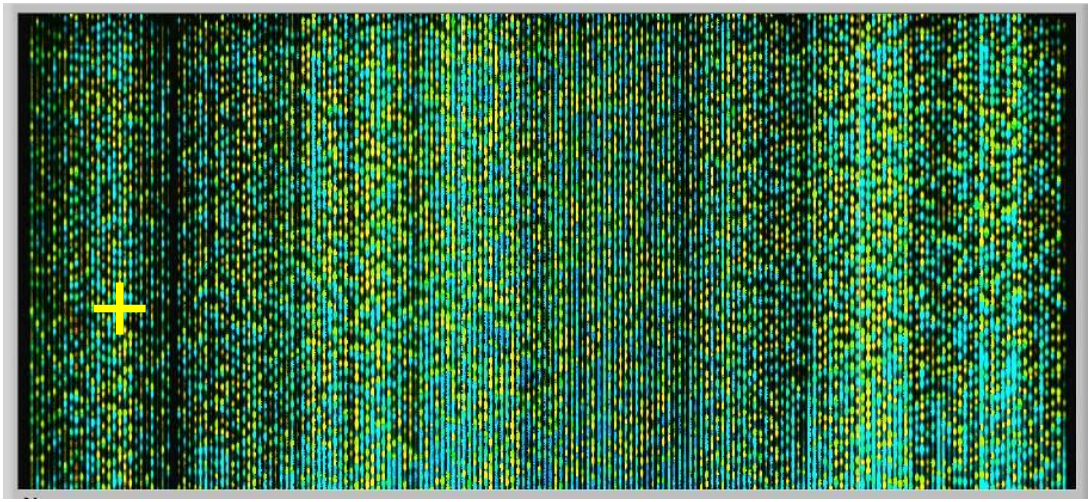
RAS



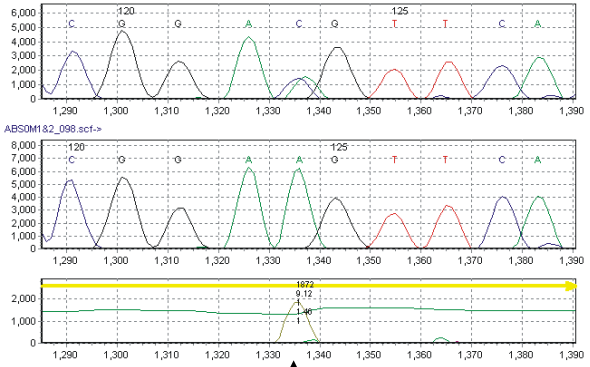
HerB

La patologia neoplastica e' dettata dai geni coinvolti prima che dall'organo colpito

Analisi della sequenza del DNA
(oncogeni codificanti tirosina cinasi del paziente XX)

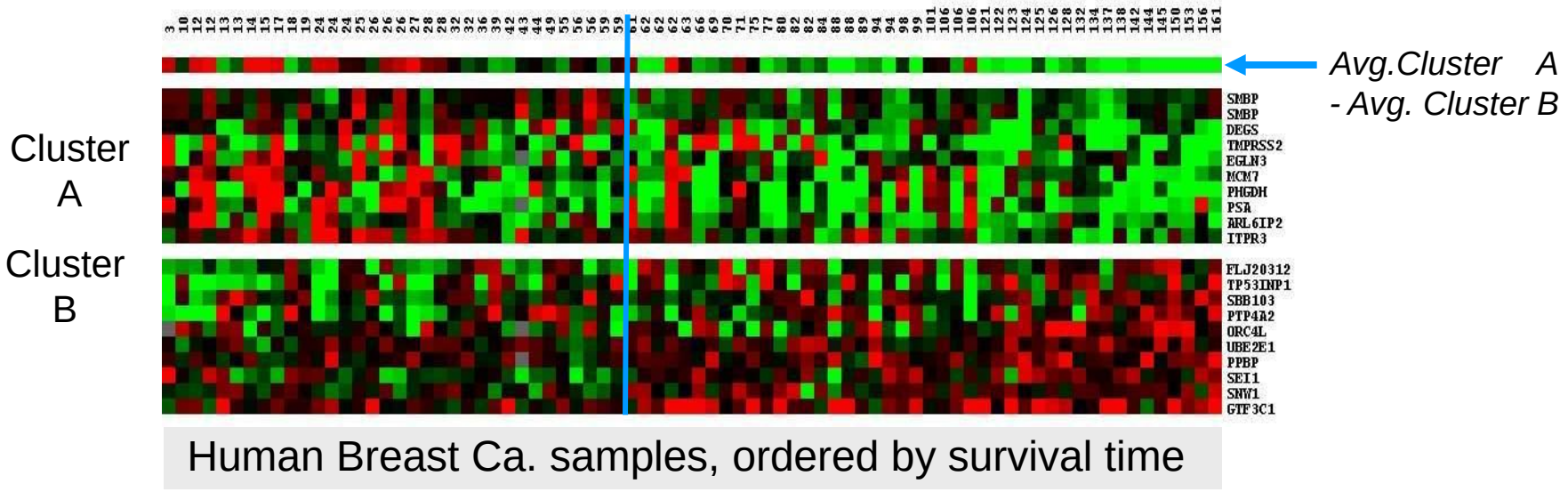


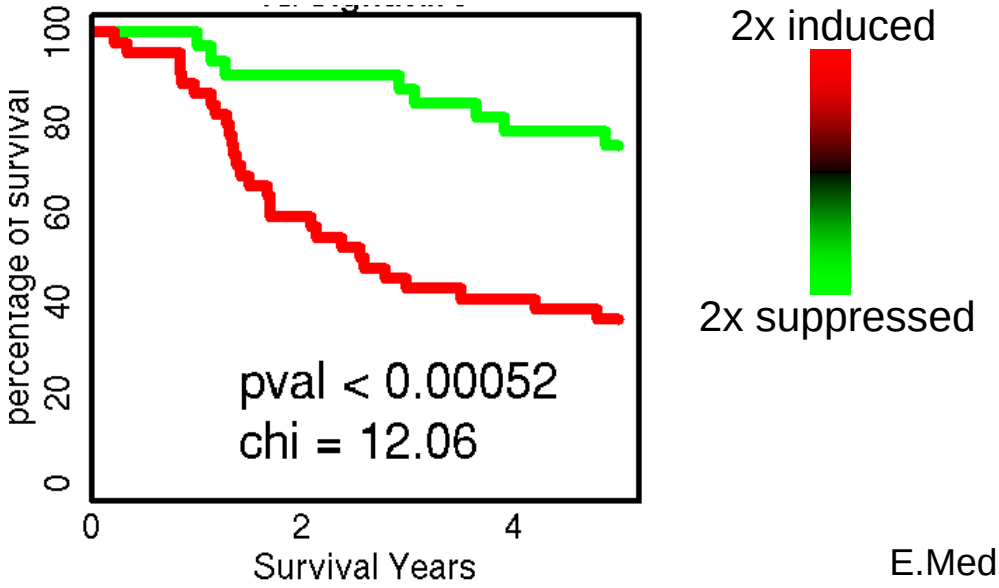
Oncogene
MET



mutazione

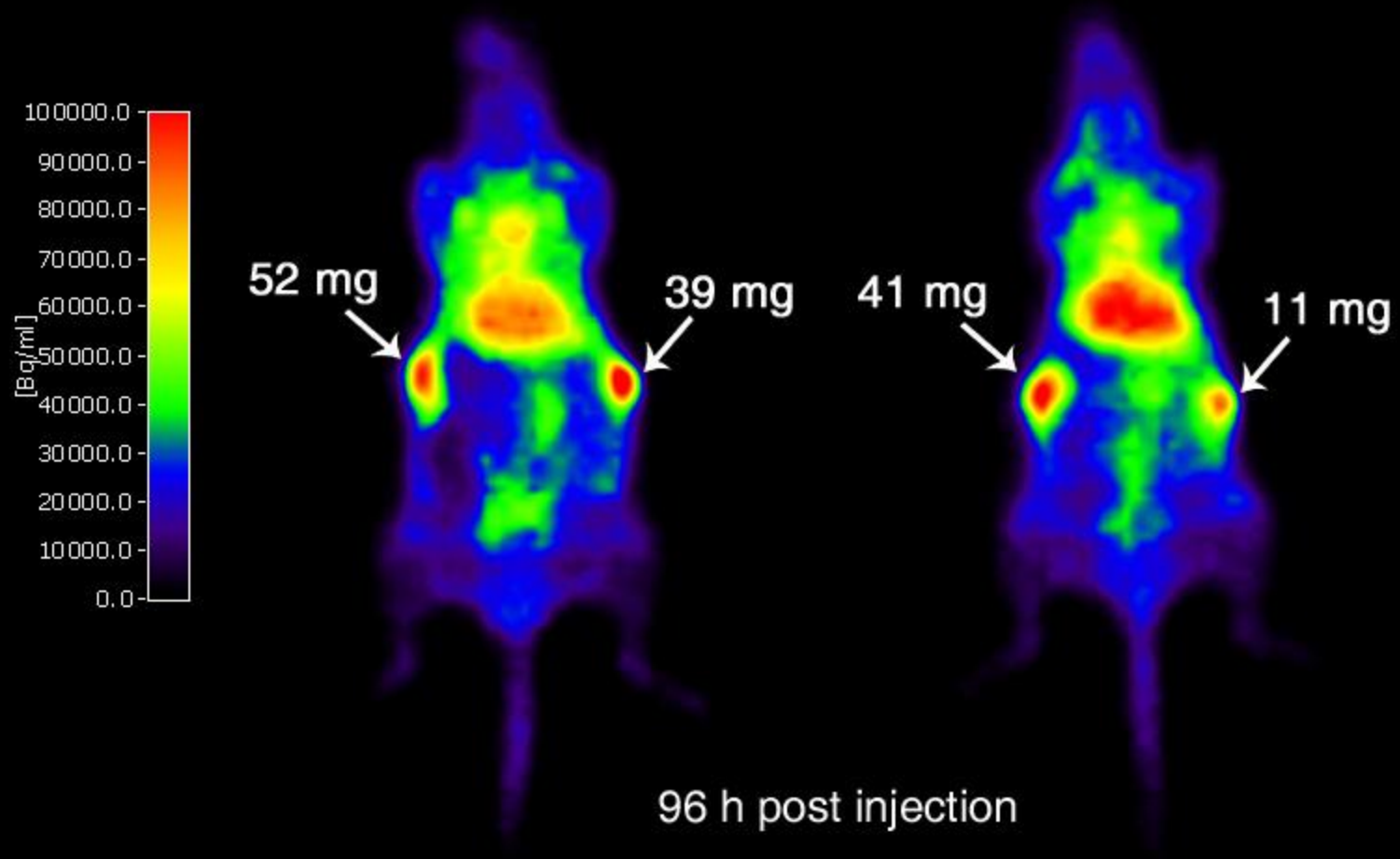
THE ‘MET-DRIVEN INVASIVE GROWTH SIGNATURE





E.Medico *et al.*(unpublished)

PET Scan, ^{89}Zr labelled DN-30 Met Monoclonal Antibody



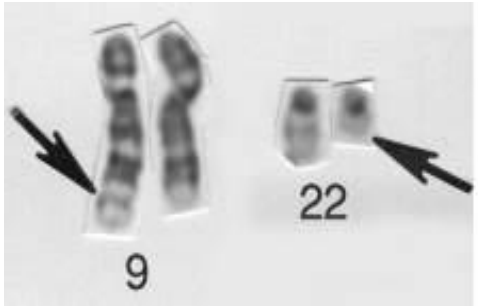
G.Van Dongen *et Al*, 2008 *Journal of Nuclear Medicine and Molecular Imaging*

6 - La “Target” Therapy

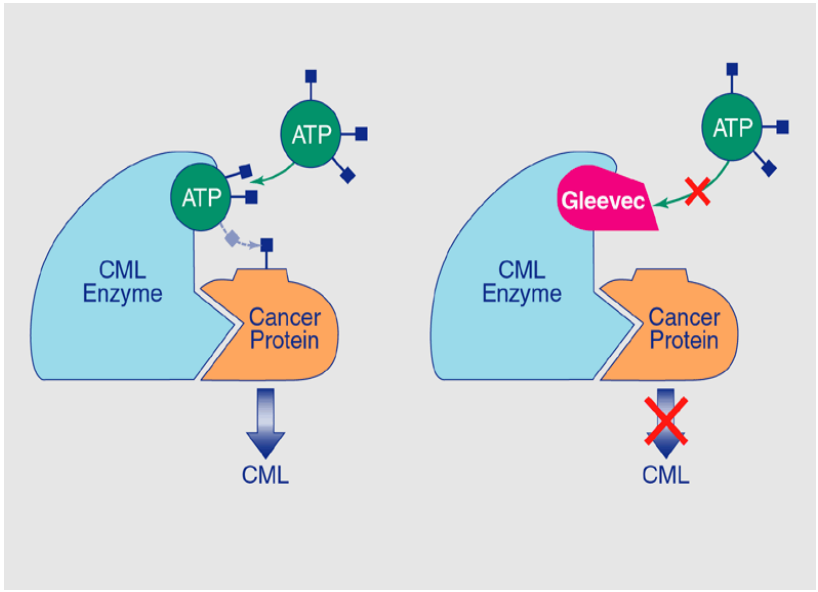
1. La terapia deve essere indirizzata contro il prodotto dei geni mutati
   (“target therapy”)

2. La terapia e’ efficace solo se il gene e’ mutato, amplificato o altrimenti deregolato (“loop” autocrino)

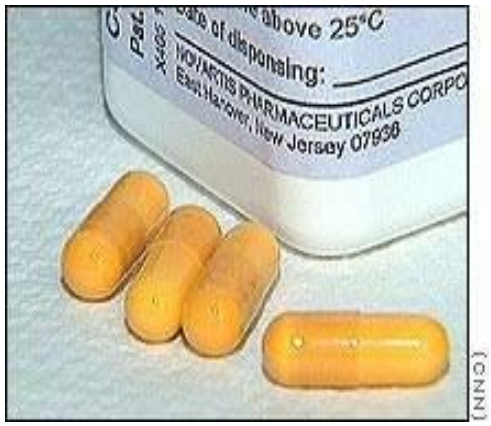
Terapia Mirata, con farmaci “intelligenti”



Lesione genetica
(riarrangiamento *Bcr-Abl*)



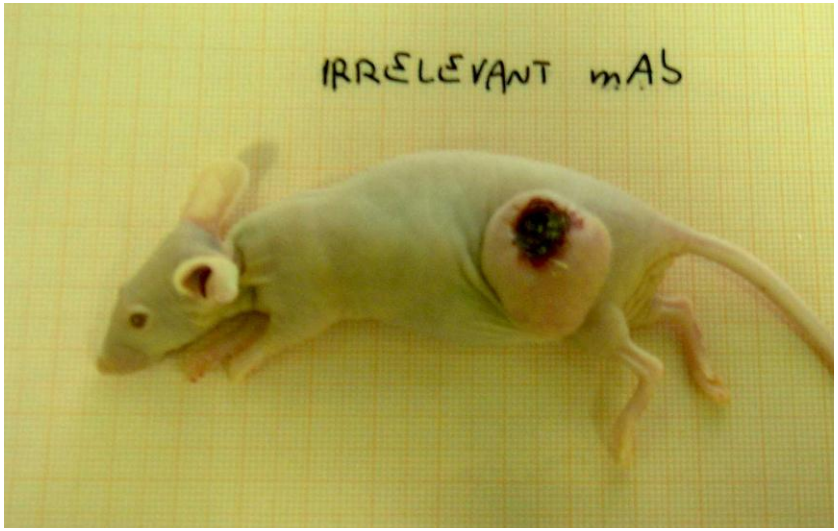
Farmaco “razionale”
(‘*Gleevec*’)



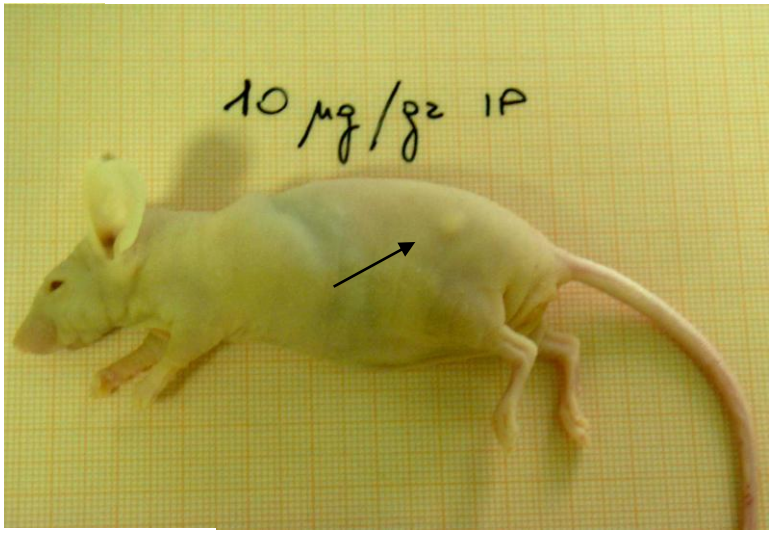
Terapia mirata

Exogenous administration of DN-30 MAb “Metheresis© ” inhibits tumor growth and metastasis

Athymic nu/nu mice, transplanted with Human Breast Carcinoma (MBA-β4)



Irrelevant Mab

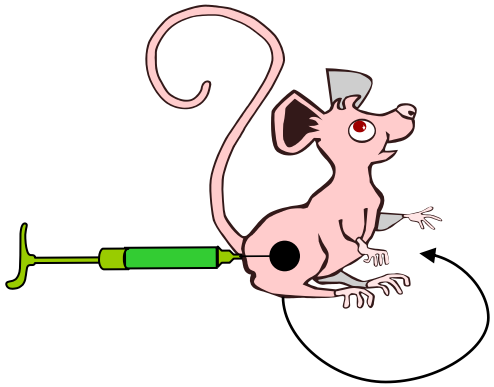


Mab DN30

Petrelli, A. *et al., Proc. Natl.Acad Sci. US: 2006, 28, 5090-5095*

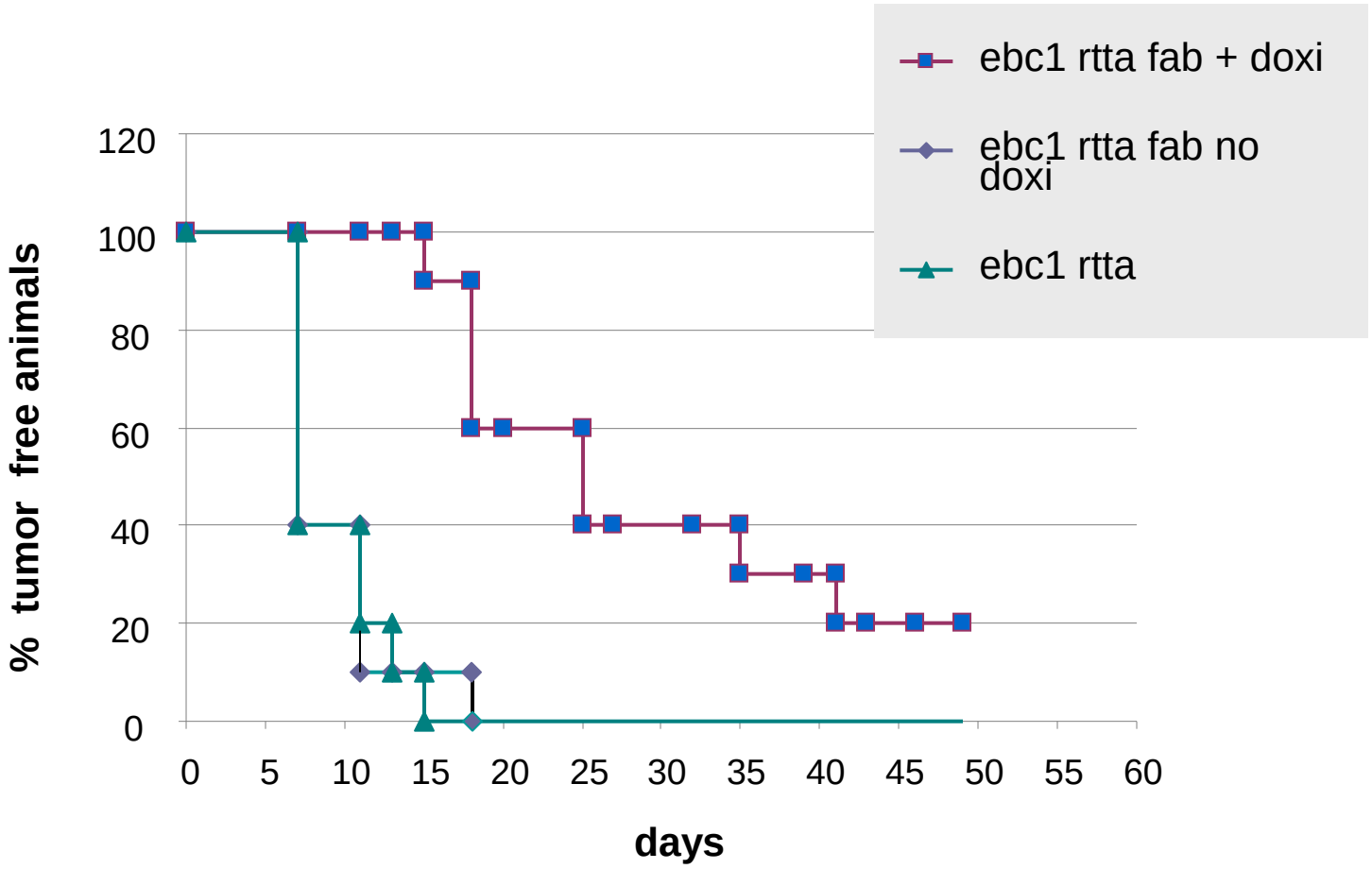
Gene Therapy with MET antibody

Bi-cistronic Lentiviral vector
carrying the cDNA
for H and L chains of DN30

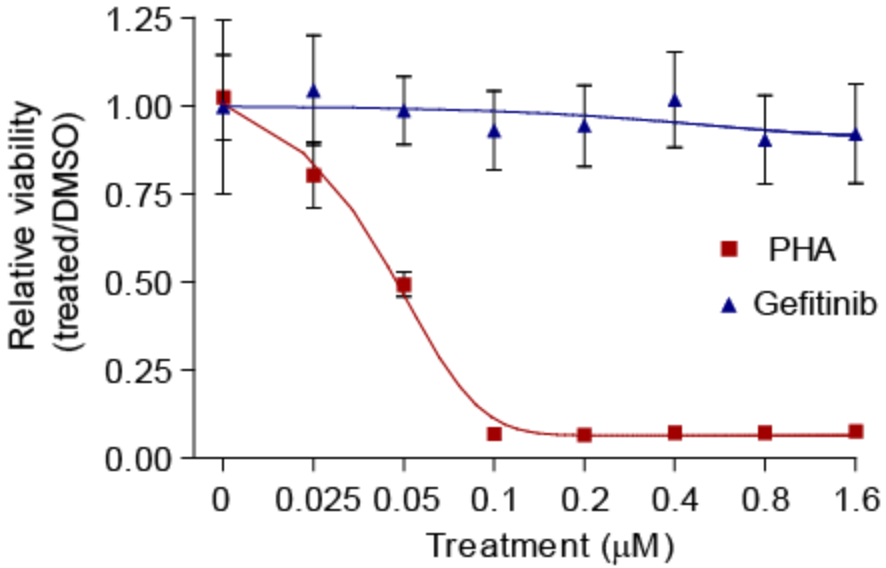


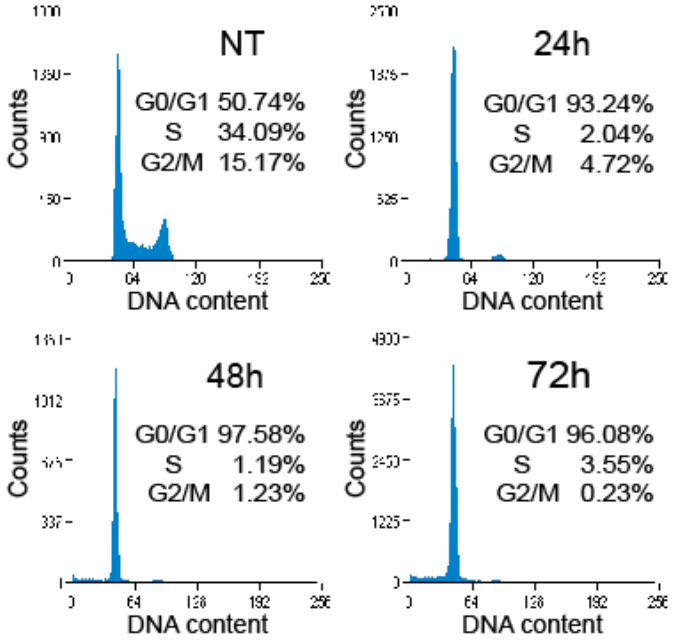
Gene transfer into the tumor:
Cancer cells produce the Monoclonal Antibody

Gene transfer of tat-inducible DN30 RF *Met* antibody inhibits growth of EBC-1lung Ca. xenotransplants



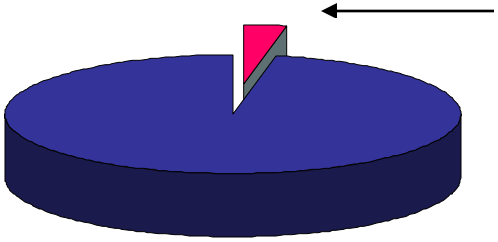
In vitro theraphy of Met–addicted human gastric Ca to a specific kinase inhibitor (small molecule)





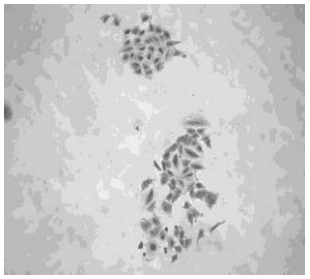
A. Bertotti, L.Trusolino et al., *Science Signaling*, 2009

MET response correlates with gene amplification



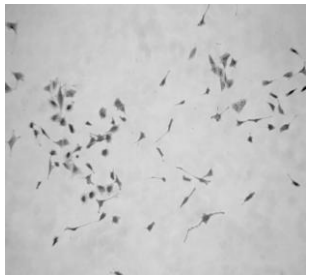
< 3 %
ADDICTION

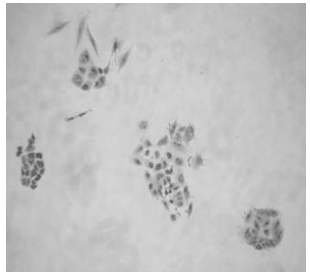
97 %
EXPEDIENCE



Hypoxia

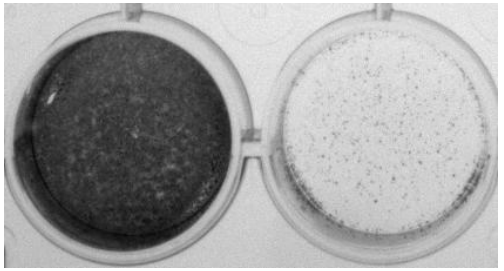
(or HGF)





PHA-665752

Cell Line	MET copy N
EBC-1	5.8
MKN-45	6
GTL-16	6.1
HS746T	6.3
SNU5	5.6
NCI-H1993	5.2



PHA-665752

Conclusione:
‘ *L’oncologia molecolare clinica* ’

1. Il cancro e’ una malattia genetica somatica che origina dalle cellule staminali

2. I geni coinvolti sono una manciata (per lo piu’ gia’ noti)

3. La diagnosi deve identificare la natura della lesione genetica (oltre che la cellula e il tessuto coinvolti)

4. La terapia deve essere indirizzata contro il prodotto dei geni mutati (“*target therapy*”)

5. La terapia e’ efficace solo se il gene bersaglio e’ alterato

Evoluzione della ricerca
IRCC (Torino) 1996 - 2010

Ricerca di base

Ricerca Pre-clinica

Diagnostica Molecolare
e Nuove Terapie“Target”

1996 ⟶ 2010

"*La Ricerca di oggi e' la Medicina del domani*"

Istituto per la Ricerca e la Cura del Cancro

Sostenuto dal fondo '5 per mille'

dell'Associazione Italiana Ricerca sul Cancro (AIRC)