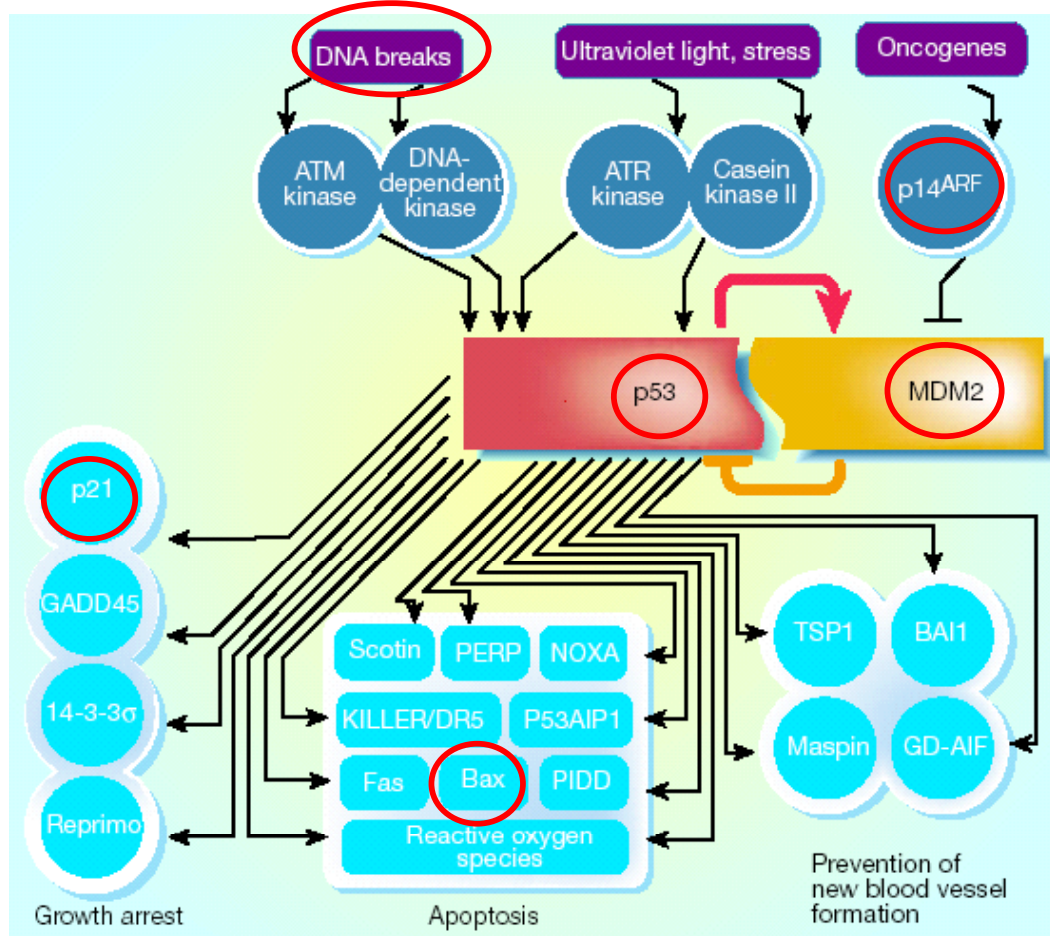


Lecture #38 – 12/7/01 – Dr. Kittlesen

molecular biology and medicine

201 12-7-01

- novel cancer therapies, strategies targeting p53
 - replace: gene therapy
 - repair using small molecules:
 - STI571, example of recent success
 - building a “molecular prosthesis” for p53
 - target by p53 absence:
 - defective adenoviruses (ONYX-015)
 - triggering death using adeno-associated viruses



Box 1 Using p53 to kill cancer cells

The p53 protein is a tumour suppressor — it keeps cell numbers down by stopping cells from multiplying or by promoting cell death. Loss of p53 occurs in most human cancers, so it would be useful to be able to restore its function. Several innovative strategies have been suggested:

- 1 ● Introduce normal p53 genes into a cancer cell with mutant p53.
- 2 ● Introduce a small compound

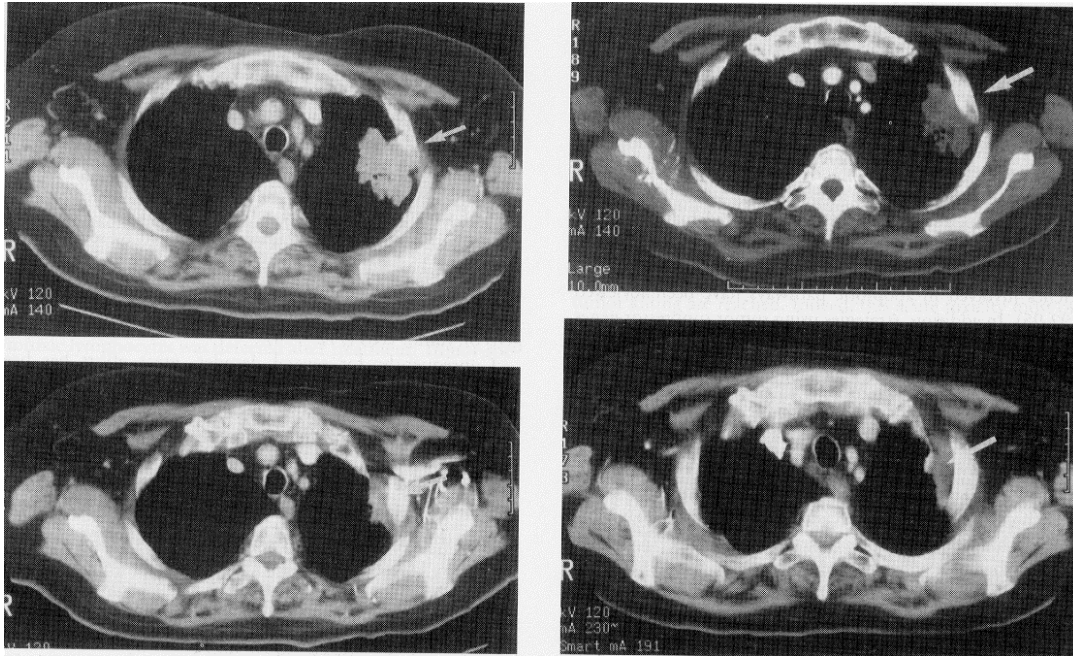
that converts mutant p53 proteins from an abnormal to a normal shape.

- Add a protein that attaches itself to mutant p53 and kills cells.
- Stimulate the host's immune response to mutant p53 peptides.
- Introduce drugs that disrupt the interaction between the MDM2 or E6 proteins and p53. (MDM2 and E6 negatively regulate p53; they are present at abnormally high levels in

some cancer cells, so 'quench' any normal p53.)

- 4 ● The strategy described by Raj *et al.*³: introduce the adeno-associated virus, which mimics damaged DNA. Cells with mutant p53 cannot activate the usual p53-dependent 'checkpoint' that is induced by DNA damage, and eventually die.
- 3 ● Infect cells with viruses that can replicate only in cells without normal p53; the viruses kill these cells. **B.V. & K.W.K.**

gene therapy: intratumoral injection of recombinant adenovirus (replication deficient) expressing wt p53

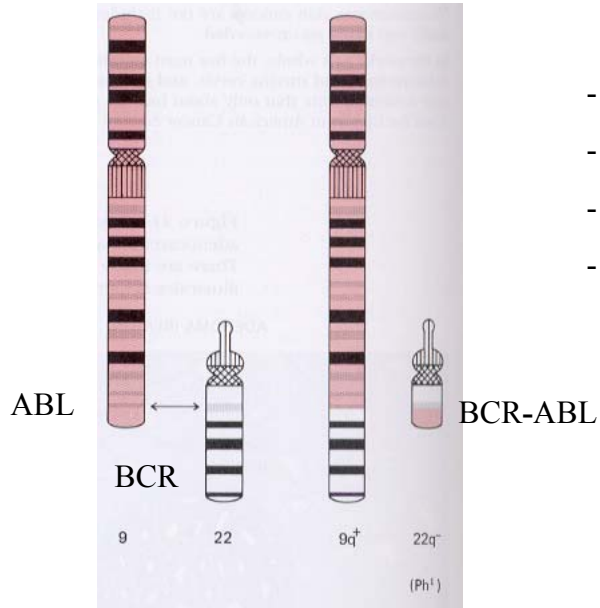


problem with strategy: targeting, especially metastasis

using of small molecules to
inhibit, even repair, proteins

- advances:
 - production, delivery, stability, history
- example: inhibiting “gain of function”
 - the Philadelphia chromosome and STI571

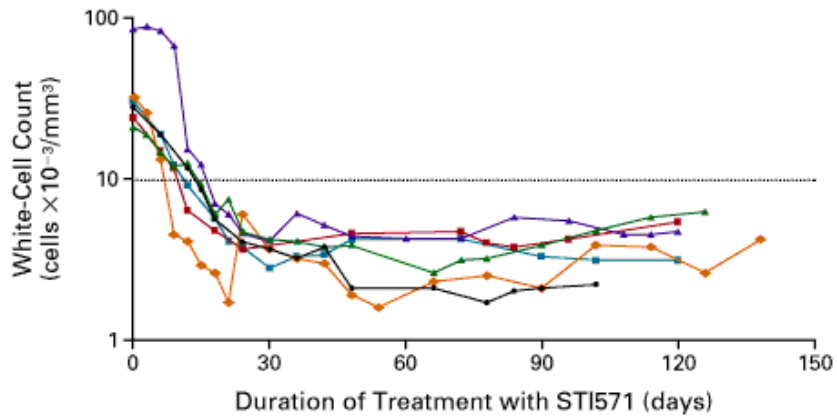
Philadelphia chromosome (observed in chronic myeloid leukemia- CML)



- predisposing factors
- translocation mechanism
- result
- evidence for significance

Alberts, et al., Molecular Biology of the Cell, 2nd ed. p 1190

WBC count in 6 human patients following STI571 therapy



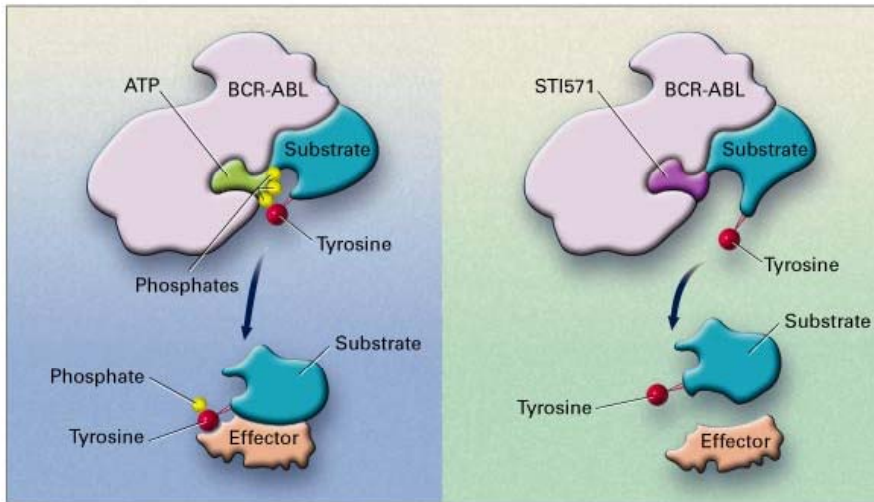
New England Journal of Medicine, 4-5-01

TABLE 3. HEMATOLOGIC RESPONSES.

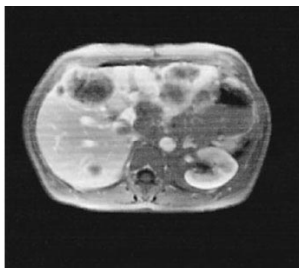
DOSE (mg/DAY)	ALL	PATIENTS WITH	PATIENTS WITH
	PATIENTS	RESPONSES	COMPLETE RESPONSES
	no.		no. (%)
25 or 50	6	2 (33)	0
85	4	2 (50)	1 (25)
140	3	3 (100)	1 (33)
200 or 250	16	16 (100)	9 (56)
300–1000	54	54 (100)	53 (98)
Total	83	77 (93)	64 (77)

New England Journal of Medicine, 4-5-01

model for STI (signal transduction inhibitor) 571

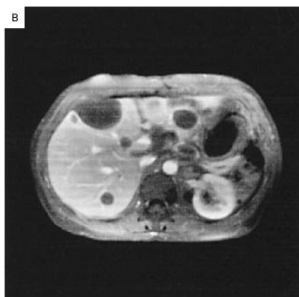


New England Journal of Medicine, 4-5-01

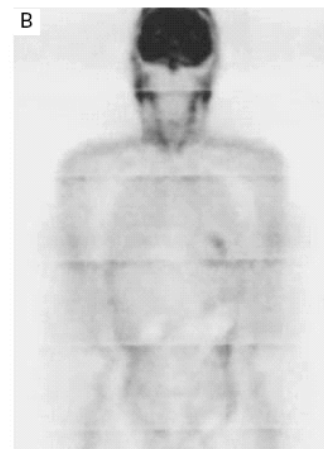
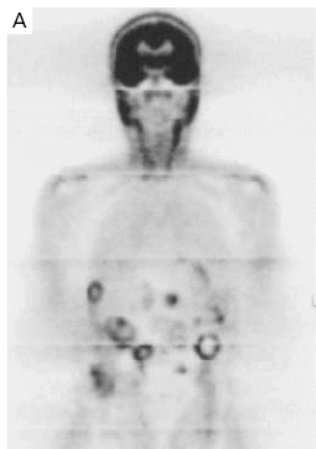


MRI

STI571 in one patient with “gain of function” c-kit defect (not Bcr-Abl)



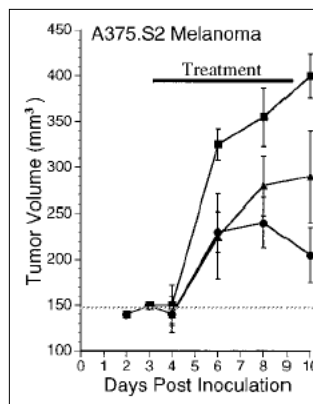
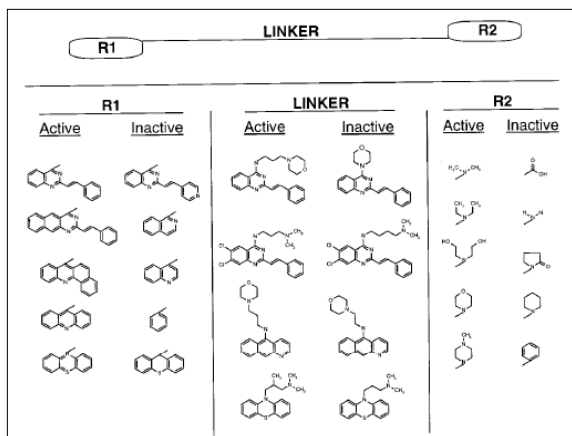
PET



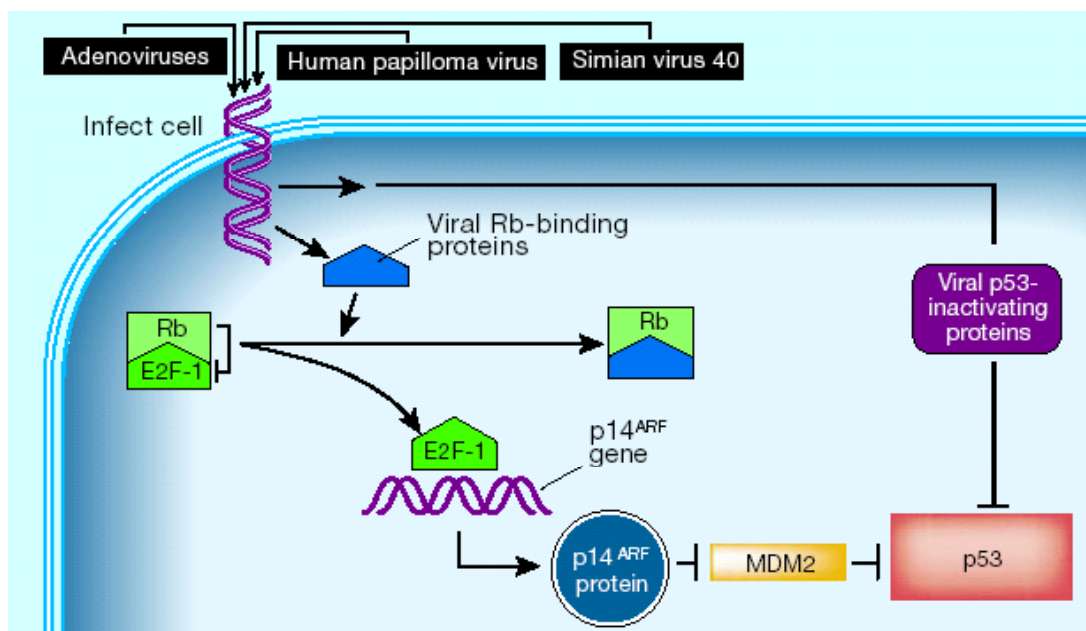
New England Journal of Medicine, 4-5-01

small molecule therapy for p53 defects: not inhibit “gain of function”, but *repair* “loss of function”

- common p53 defects



targeting *absence* of p53 function



ONYX-015 (defective adenovirus) strategy
 - controversy, and problems (neut Abs)

targeting *absence* of p53 function

adenoassociated virus

- low immunogenicity
- ssDNA
- “damage response”
- results

