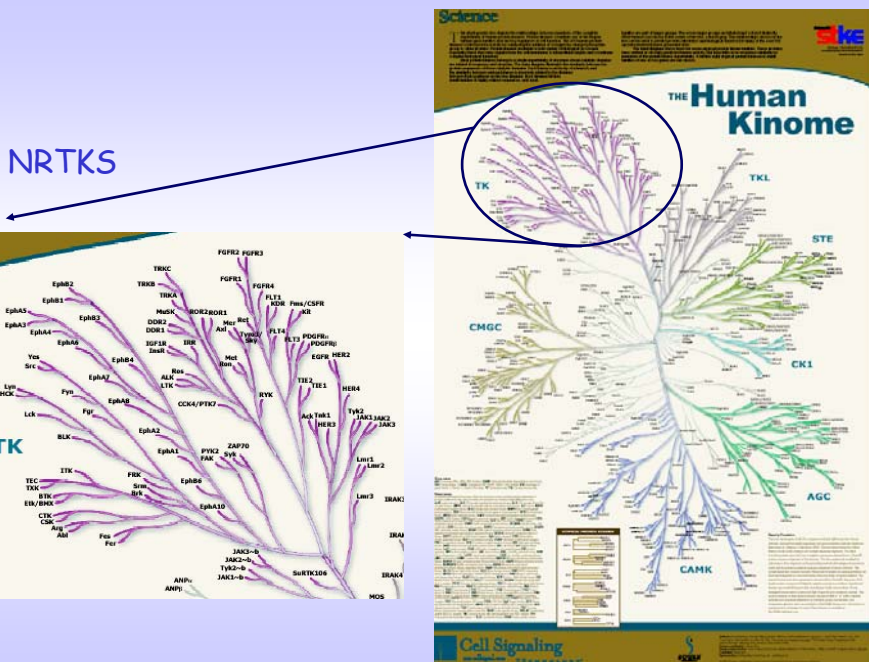


# Non-Receptor Tyrosine Kinases

**EMBO** Lecture Course  
"Receptor Mechanisms & Signal Transduction"



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## AIMS

- ➔ Take a close look at similarity within Src-family and other members of NRTK
- ➔ Phosphorylation site mapping : Models vs. Reality
- ➔ Comparison with receptor tyrosine kinase

## ***CYTOPLASMIC NON-RECEPTOR TYROSINE KINASE FAMILY***

### ***CELLULAR LOCALISATION***

Soluble components

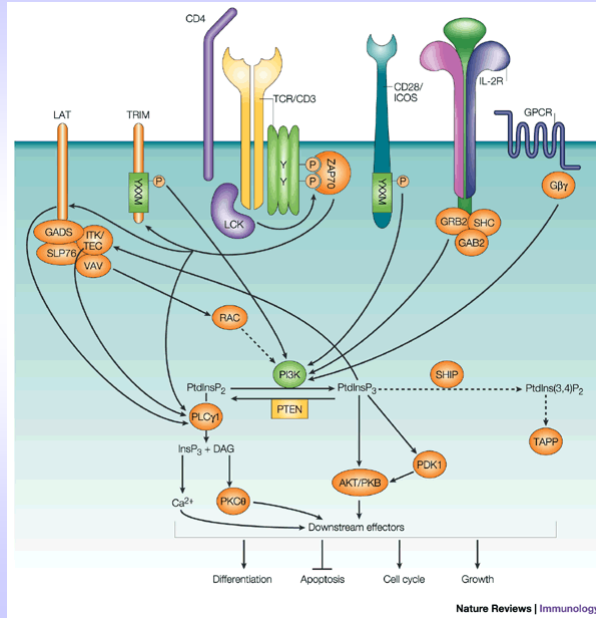
Membrane-associated

### ***FUNCTIONAL ROLE***

Cell proliferation-differentiation-death

Receptors that recruit NRTKs:  
TCR, BCR; IL-2R, Ig-receptors,  
erythropoietin and prolactin receptors

## Signalling in T cells mediated by src kinases



## Cytoplasmic Tyrosine Kinases

SRC, YES, FYN,  
LYN, LCK, BLK,  
HCK, FGR, YRK

FRK (MCK3), BRK  
SRM, SAD

BTK, ITK, TEC  
MCK2 (BMX)  
TXK

CSK,  
CTK (MCK1)

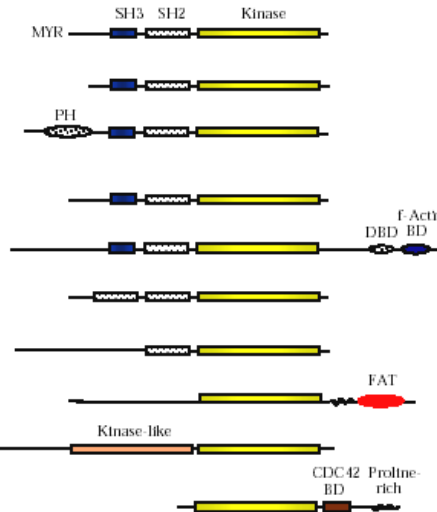
ABL, ARG

ZAP70, SYK

FAK, PYK2

JAK1, JAK2,  
TYK2, JAK3

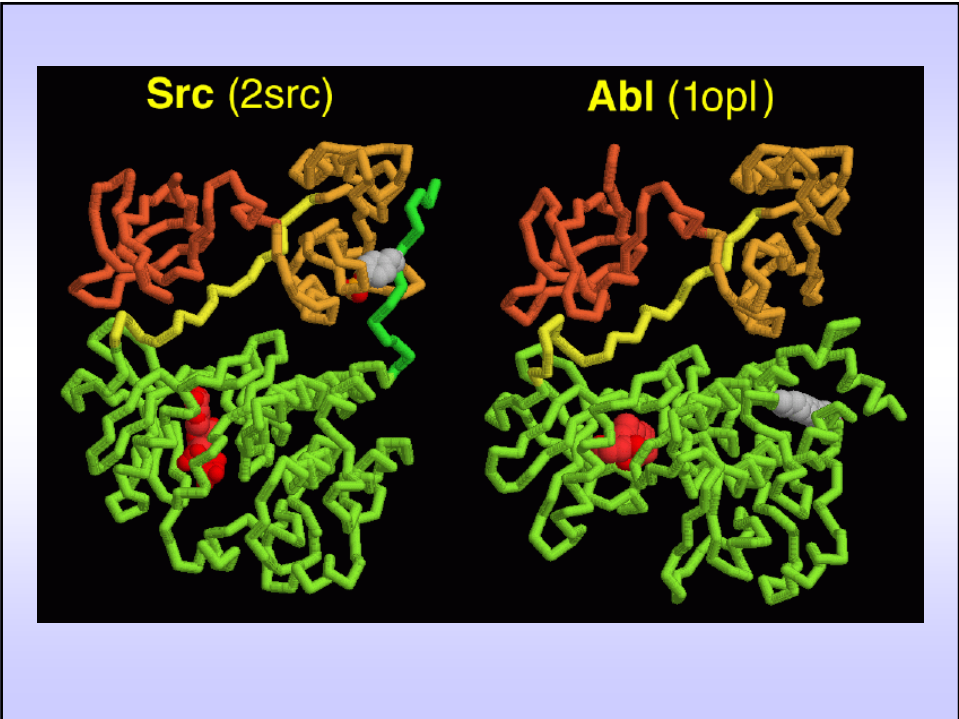
ACK, ACK2



src-related

others





**PHOSPHORYLATION SITE MAPPING**  
Prediction vs. reality

cSrc

MAPPED

REAL

Y 416  
(ProSite)

Y 416 (activation loop)  
Y 527 (CSK site)

## Abl- Phosphorylation sites

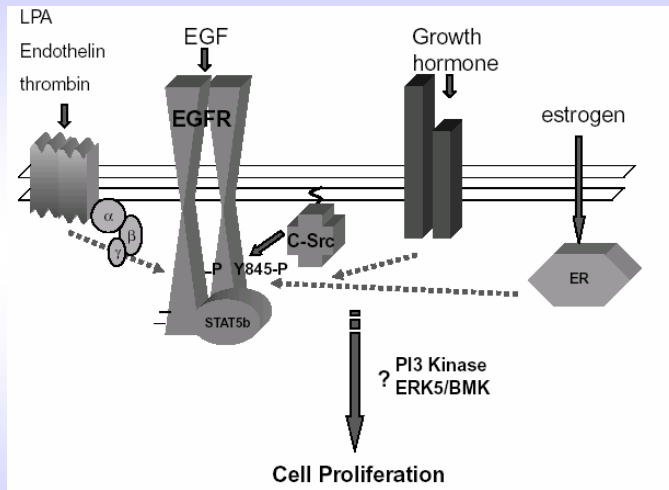
Real	NetPhos	ProSite	ScanSite stringency
Y 125			
Y 134			+
Y 204	+		
Y 245			+
Y 251			
Y 272			+ +
Y 276	+		+
Y 412			

## Phosphorylation Mapping

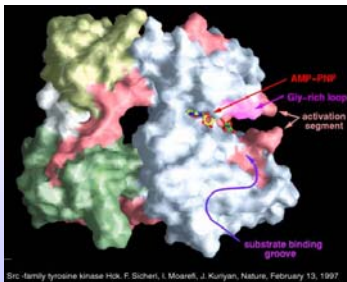
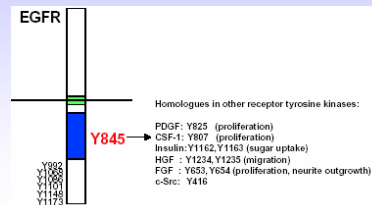
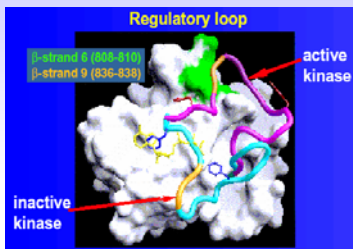
Problems to be aware of:

- ➔ Models might miss phosphorylation sites to bias in the mathematics underlying the program
- ➔ How can you be sure to have mapped all P- sites and exclude the false positives from mapping?? (look at 3D if available → buried residues unlikely to be accessible for kinases)
- ➔ Experimental models: in vivo vs. In vitro use of fusion proteins  
→ influence on structure and accessibility of residues ?

## Receptor Tyrosine Kinase-EGFR



## EGFR and c-Src synergism



-Members of both families are overexpressed in ~70% of human breast cancers

-Tyr 845 shares high degree of homology among all tyrosine kinases

-Tyr 845 phosphorylation is mediated by cSrc...a unique characteristic

## Receptor (Her2/Her3) and non-receptor (c-Src) tyrosine kinase domain similarities

EGFR.kin_dom	1	PHVSRLLGICLTSTVOLVTCQMPVGGCLLDVYVREHKDNHGSQYLLNWCVOIAKGMNVLED
HER2/ErbB2.kin_dom	1	FVYSRLLGICLTSTVOLVTCQMPVGGCLLDHVRENRGRHLSGSDLLNWCVOIAKGMNVLED
HER3/ErbB3.kin_dom	1	AEIVRLLGICPGSSTQLVTCYVDFGSLLDHVREHRCRLEGFQCLLNWCVOIAKGMNVLEE
SRC.kin_dom	1	EKLIVQLIAVYVSEEPYIVVTEHMSRSGSLDLELKGETGRYRRLFCQVMAAQLASGMAMVGR
EGFR.kin_dom	60	RRLVHRDLAARNVLVKTPQHVKHTDFGLAKLLGAEKEKYHAEGGKVPKWMMALESILHR
HER2/ErbB2.kin_dom	60	VRLVHRDLAARNVLKSPNHVKHTDFGLARLLIDEIETVHADGGKVPKWMMALESILRR
HER3/ErbB3.kin_dom	60	HGIVHRDLAARNVLKSESCVQVADDFGADLPPDKKLLYSEARKTPKWMMALESIFHG
SRC.kin_dom	61	MNYVHRDLAARNLVGENLVCKVADDFGLARLLEQNEYTARQCAKPKPKWMALESILVY
EGFR.kin_dom	119	RYTHQSDVWSYGVTVWELMTFGSKPYDGPASEISSLLEKGERLPOPPICTIDVYIMMV
HER2/ErbB2.kin_dom	119	RRYTHQSDVWSYGVTVWELMTFGAKPYDGPAREIPDLLEKGERLPOPPICTIDVYIMMV
HER3/ErbB3.kin_dom	119	KRYTHQSDVWSYGVTVWELMTFGAEPYAGIRLAEVDPDLLEKGERLPOPPICTIDVYIMMV
SRC.kin_dom	119	RRTIRSDVWSYGVTVWELMTFGKRVYPCVQVNRVLDQVRCYRMECPPECPESEHDLVC
EGFR.kin_dom	178	KCWMIDAEKSRPRFRELVEFS
HER2/ErbB2.kin_dom	178	KCWMIDAEKCRPRFRELVEFS
HER3/ErbB3.kin_dom	178	KCWMIDENIRPTFKELANEE
SRC.kin_dom	178	CKWRKEEERPTFELVCAE

The ErbB signalling network →

