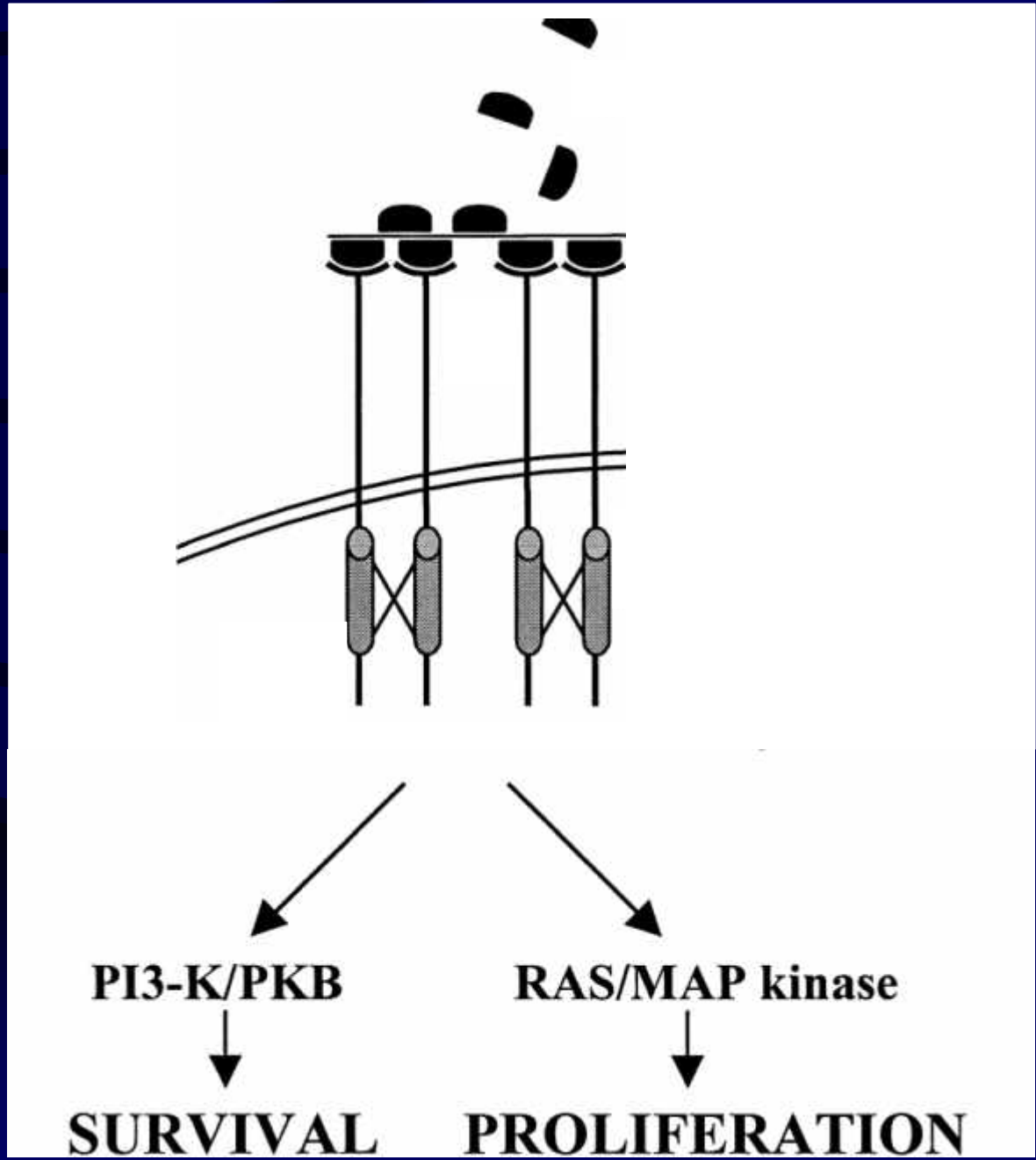


# Tyrosine kinase receptors

Husam, Elles, Akin & Liisa

# Tyrosine kinase receptors

- Ligand binding leads to dimerization, phosphorylation and activation of the receptor signaling pathways
- This leads to proliferation and differentiation of cells



# Structures

Met



ErbB1



PDGFR



ErbB4





# Kinase domains

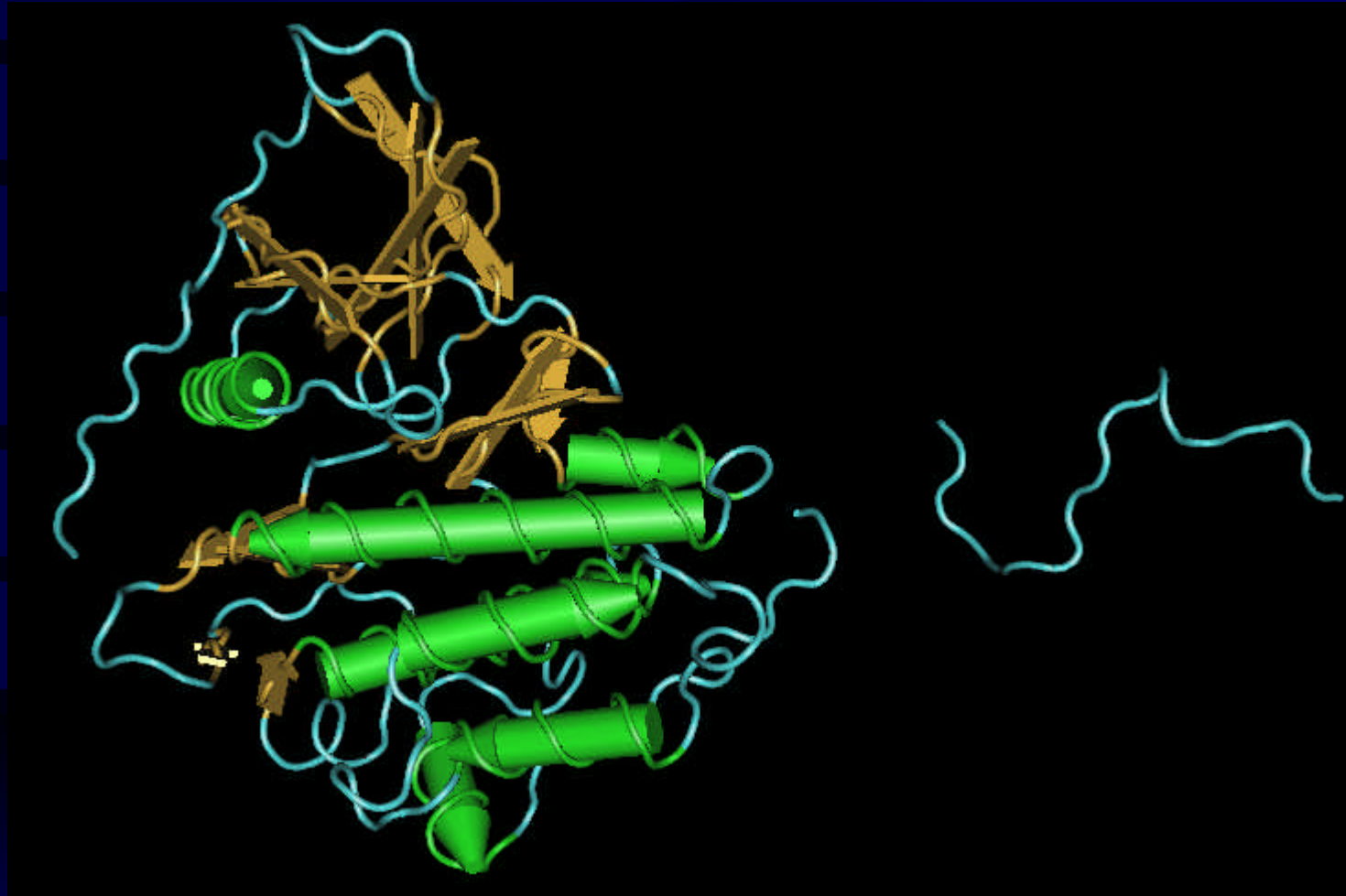
	1	10	20	30	40	50	60	70	80	90	100	110	120	130																																																																										
	-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----																																																																																							
Met											VHFNEVIGRGHFGCVYHG	TLL-DNDGK	KIHC	AVKSLNR																																																																										
EGFR											FKKI	KVLGSGAFGT	VYKGLM	WPEGEK	VKIPVAIKELRE																																																																									
ERB4											LKRY	KVLGSGAFGT	VYKGLM	WPEGET	VKIPVAIKILNE																																																																									
PDGF	VLGRTL	GSGAFG	QYVE	ATAH	GLSH	SQATM	KVAV	KMLK	STAR	SSEK	QALM	SELK	IMSH	LGPL	NVYV	LLGACT	KGGPI	YIITE	YCRY	GDLV	YLRN	KHTFL	QHSD	KRRP	PSA-EL	YSNAL	PVGL	PLPSH																																																												
Consensus	.....											lhrnk	v.g.ghfg	vy.g....	#....	kipva	.k.l..																																																																							
	131	140	150	160	170	180	190	200	210	220	230	240	250	260																																																																										
	-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----																																																																																							
Met	ITDIGE	VYSQ	FLTE	GIIM	KDFSH	PWVLS	LLG-IC	LRS	EGS	PLV	VPY----	MKNG	DLRN	FIRN	ETHN	PTVK	DLIG	FG	LQVAK	GMYL	ASK	KFVHR	DLA	ARN	CHL	DEK	FTVK	VAD	FGL	ARD	MYD	KEY	YSV																																																							
EGFR	ATSPK	ANKE	ILDE	AYVM	ASVD	NPHV	CRLL	G-IC	LTS--	TVQ	LIT	QL----	MPFG	CLLD	YVRE	HKDN	IGSQ	LLN	WCY	QIA	GMN	YLED	RRLV	HRD	LAA	RNV	VKTP	QHV	KITD	FGL	AKLL	GAE	--KE																																																							
ERB4	TTGPK	ANVE	FMD	EALIM	ASMD	PHLV	RLG-V	CLSP--	TIQ	VTQ	QL----	MPHG	CLLE	YVRE	HKDN	IGSQ	LLN	WCY	QIA	GMN	YLED	RRLV	HRD	LAA	RNV	VKSP	NHV	KITD	FGL	ARLL	GDE	--KE																																																								
PDGF	VSLT	GESD	GGYD	MSKDE	SVDY	VPML	DMK	GDV	KYAD	IES	SNYMA	PYD	NYV	PSA	P	ERTC	RATL	NE	SPV	SYM	DLV	GF	SYQ	VANG	ME	FL	ASK	NCV	HRD	LAA	RNV	LICE	GKLV	KICD	FGL	ARD	IM	RS--	NY																																																	
Consensus	.t..ge	.....	#...	n.svd	p..l.\$	IG!	!cl	.....	s.....	py.....	mp.g	lr....	#e..n	....	dL	gf..	Q!AK	GM.%	Lask..	VHRD	LAA	RNV	v\$.e...	VK!	DFGL	ARd...	de....																																																													
	261	270	280	290	300	310	320	330	340	350	360	378	72																																																																											
	-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----+-----																																																																																							
Met	HNKTG	AKLP	VKMA	LES	LQ	TQK	FTT	SDVMS	FGV	VLWEL	NR	TRG	APP	YD	VNT	F-D-	ITY	LLQ	GR	RL	QPEY	CP	PL	YV	ML	KC	WHP	KA	EM	RP	SF	SEL	V	SR	IS	AIF	ST	FI																																																		
EGFR	YHAE	GGK	YPIK	MALES	IL	HR	YTH	QSDVMS	YGV	TVWEL	NT	F	GSK	PY	DG	I	PA	S-	ISS	L	E	K	G	E	R	L	P	Q	P	I	C	T	I	D	V	Y	I	M	V	K	C	W	I	D	A	S	R	P	K	F	R	E	L	I	E	F	S	K	N	A	R	D	P	Q	R	Y	L																					
ERB4	YNAD	GGK	NP	IKMA	LE	C	I	HYR	KFT	HQSDVMS	YGV	TVWEL	NT	F	GSK	PY	DG	I	P	T	R-	IP	D	L	E	K	G	E	R	L	P	Q	P	I	C	T	I	D	V	Y	I	M	V	K	C	W	I	D	A	S	R	P	K	F	K	E	L	A	E	F	S	R	N	A	R	D	P	Q	R	Y	L																	
PDGF	ISK	G	ST	F	L	PL	K	MA	P	E	S	I	F	N	S	L	Y	T	L	SDVMS	F	G	I	L	W	E	I	F	T	L	G	T	P	Y	P	E	L	P	N	E	Q	F	N	A	I	K	R	G	Y	M	A	Q	P	A	H	A	S	D	E	I	Y	E	I	M	Q	K	C	E	E	K	F	E	I	R	P	F	S	Q	L	V	L	L	L	L	L	L	L	L
Consensus	..k.g	.klp	.KMA	LESi	.....	%t	.SDVMS	%G!	!WEL	nT	Gg	Pp	..p..	#.i	....	l..	G.R	\$	QP	..c	d..	Ye!	M	KC	W	..ka	#.RP	.Fs	#Lv	.....	sr	.....																																																								

# Docking and Y phosphorylation sites

	<b>MET</b>	<b>ErbB1</b>	<b>ErbB4</b>	<b>PDGFR</b>
<b>p85: SH2</b>	Y1334 DPLYEVM	Y948	Y1056 PPAYTPM	Y740 DGGYMD M
				Y751 SVDYVPM
				Y934 DEIYEIM
<b>Grb2: SH2</b>	Y1377 NATYVNV	Y1096	Y1202 EDEYVNE	-
		Y1114		

<b>Phosphorylation sites :</b>	<b>MET</b>	<b>ErbB1</b>	<b>ErbB4</b>	<b>PDGFR</b>
<b>pTYR</b>	1331 DPLYEVM		1056 PPAYTPM	751
	1374 NATYVNV		1202 EDEYVNE	857

# Structure



**Jennifer Stamos et al. J. Biol. Chem., Vol. 277, Issue 48, 46265-46272, November 29, 2002**

- The total sequence alignment showed almost no similarity
- The alignment of the kinase domains of the receptors did show a high similarity
- We also looked if there are similarities between the docking sites of the receptors

# Conclusions

- Multiple alignments of full length sequences is less informative than sequences of subdomains.
- Receptor tyrosine kinases share similar topology.
- ErbB family does not require phosphorylation of active site loop for full activation.
- Despite the remarkable differences in the kinase domain structure, they perform the same action.
- Different Bioinformatics tools give different results.

We Thank all the organizers of  
this lovely course!