

Complexity of estrogen dependent gene regulation

Ulrich Pfeffer

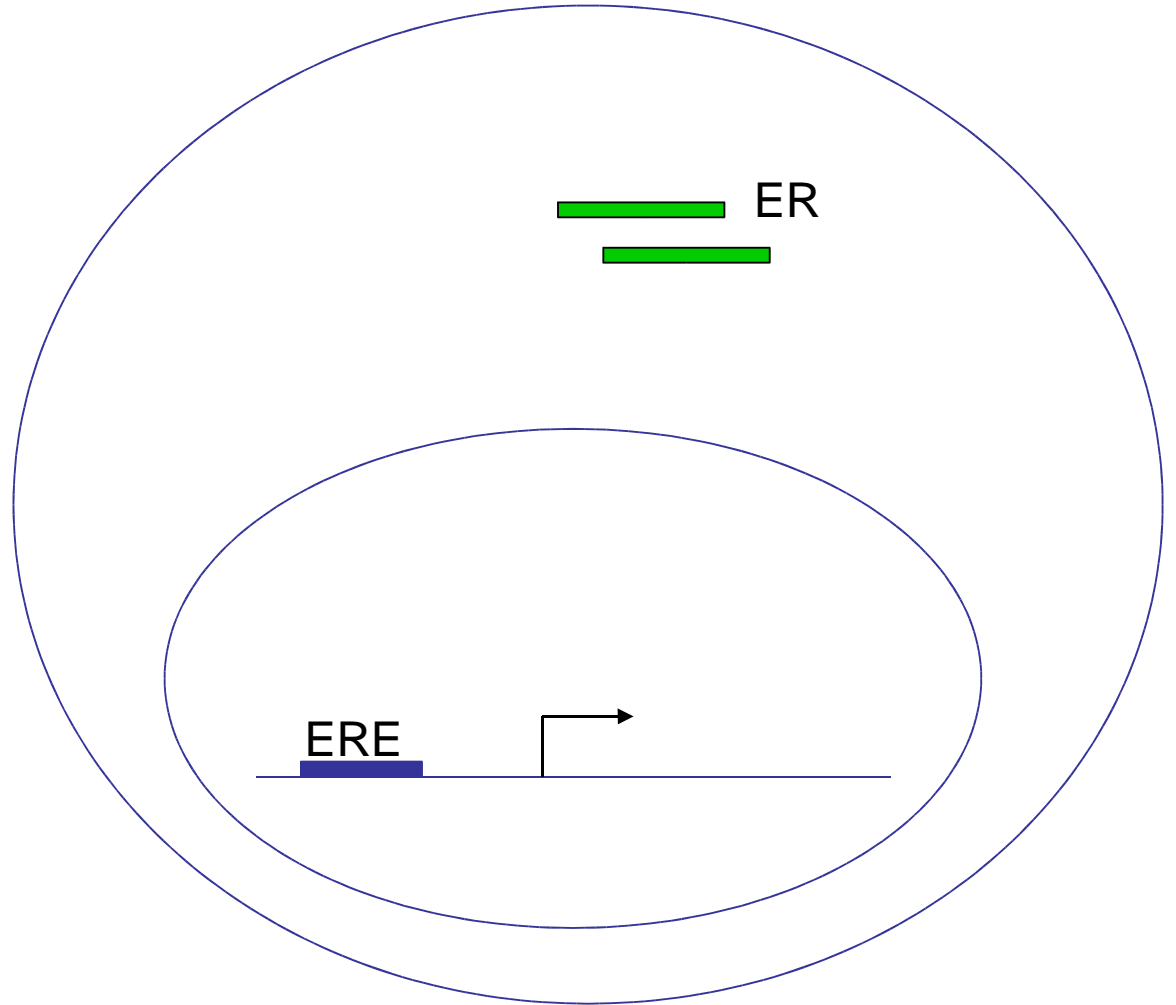
IST , Genova

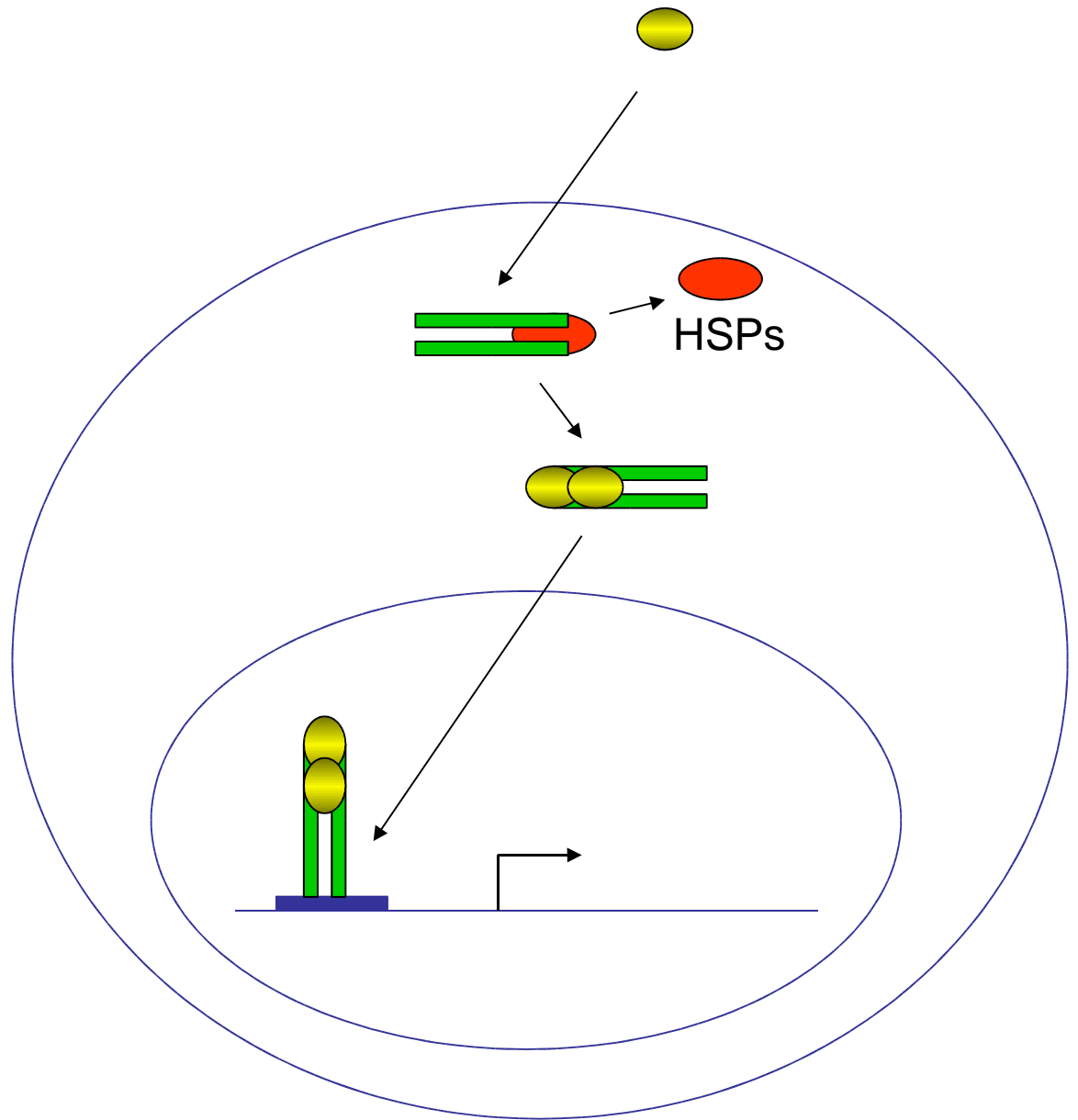
Estrogen

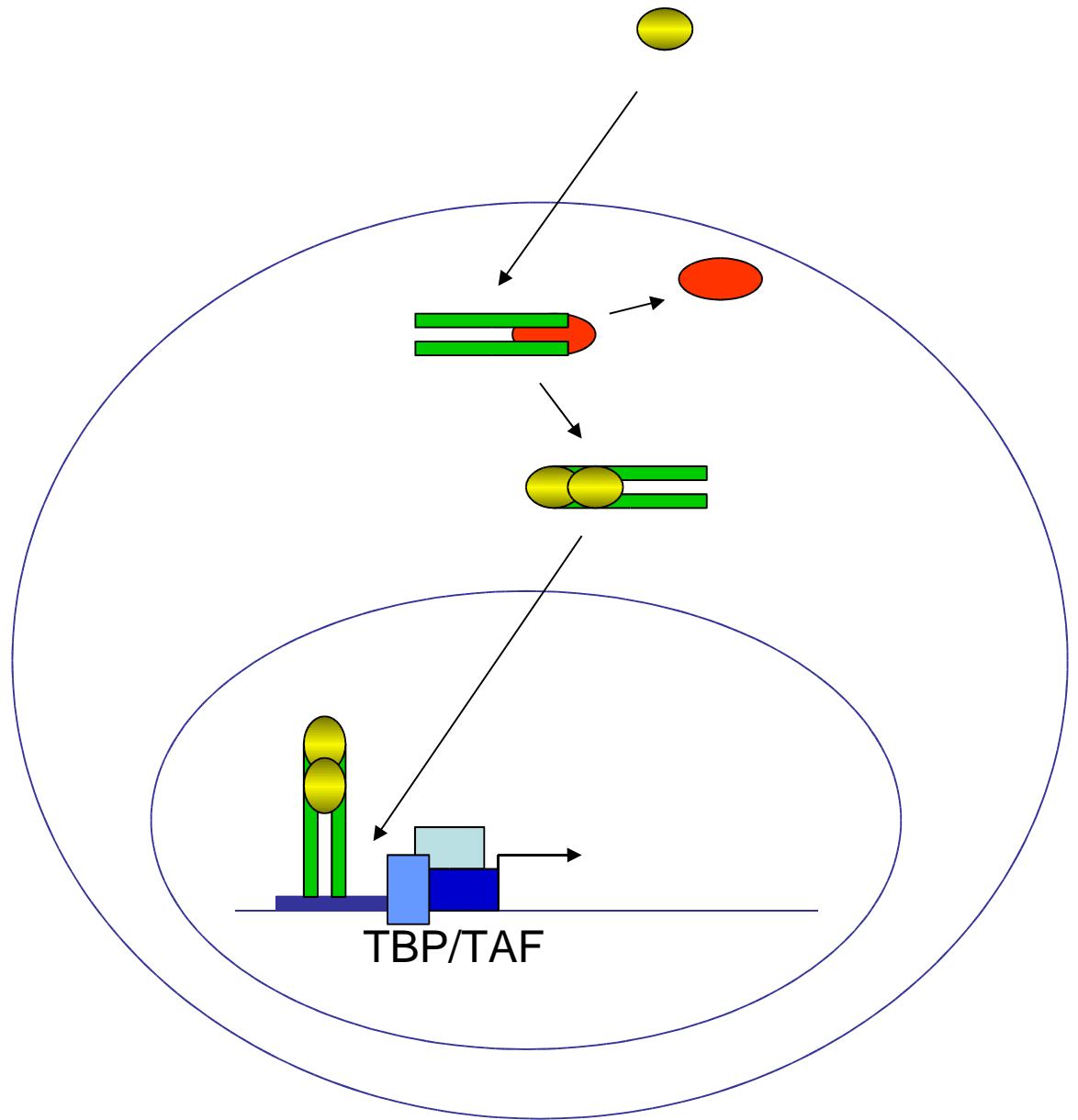


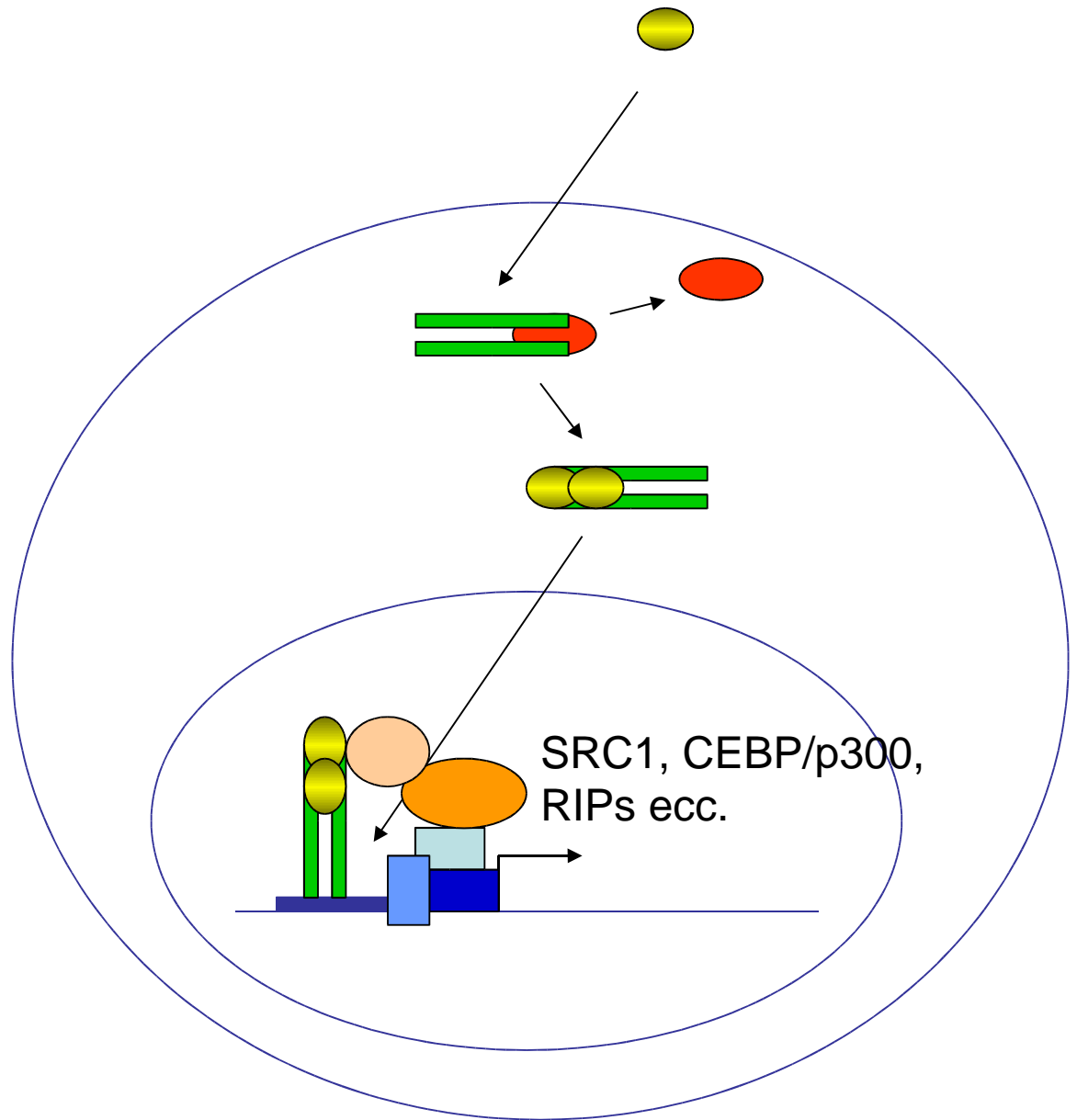
Cell proliferation

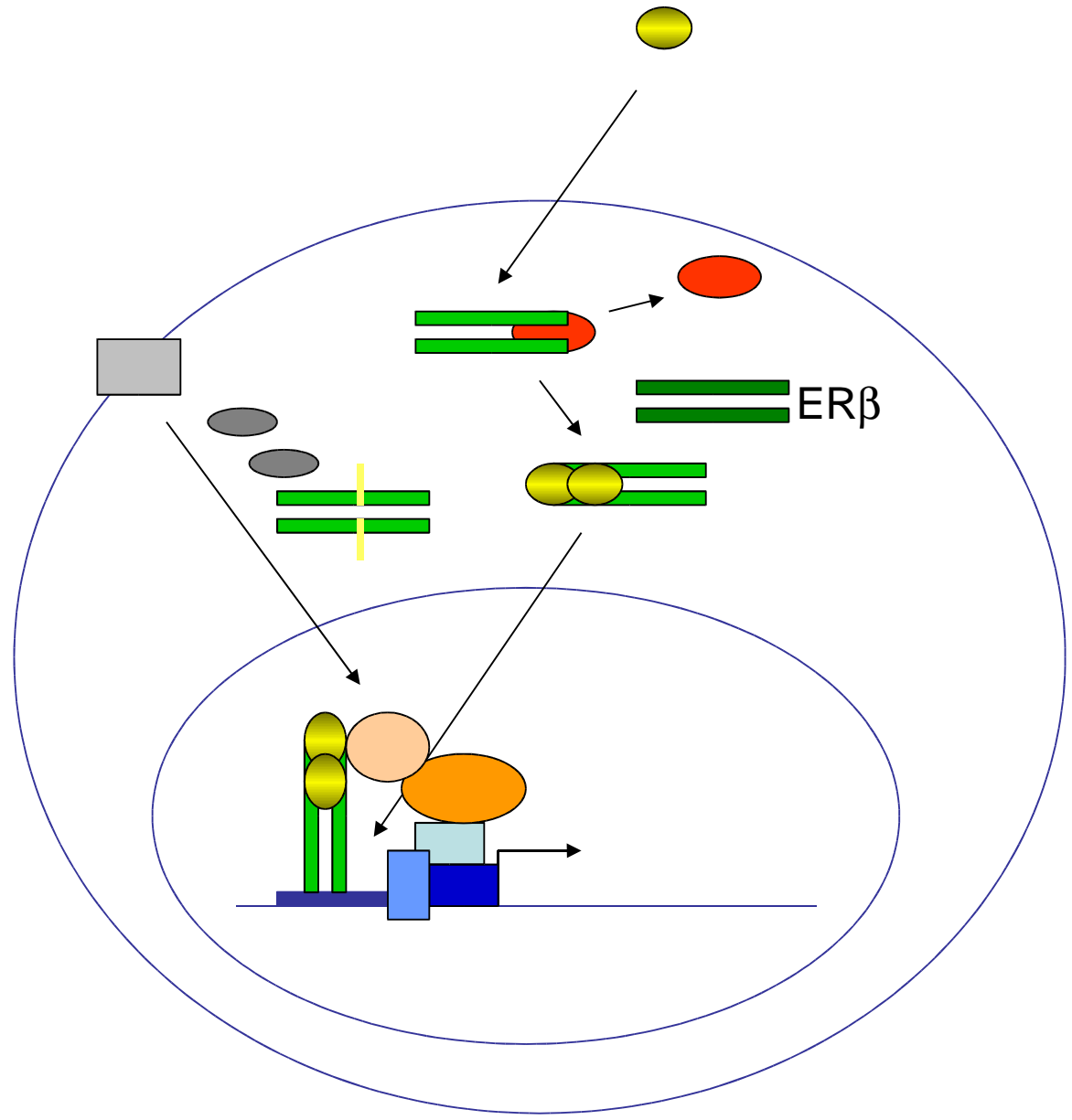
● E2

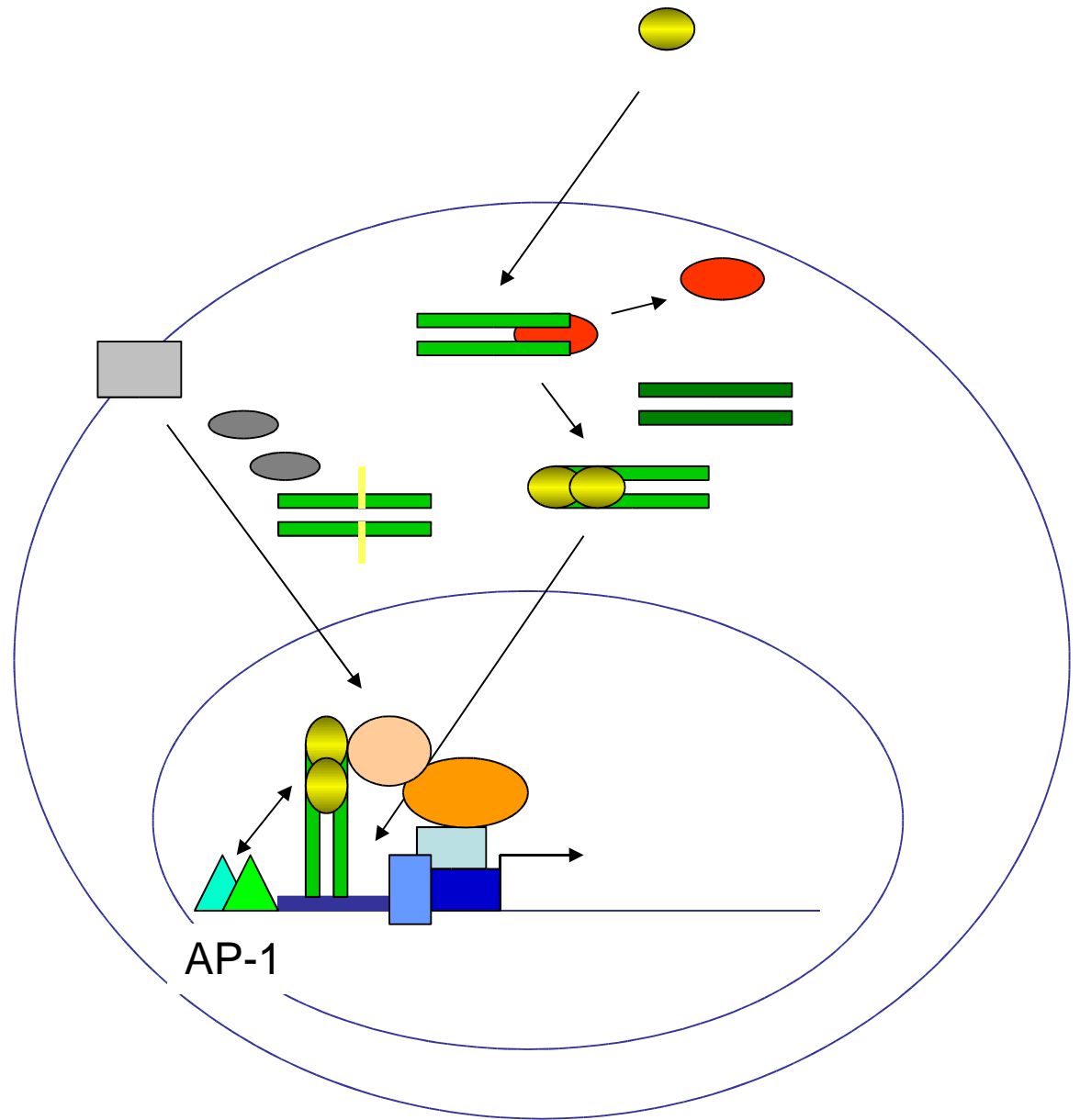


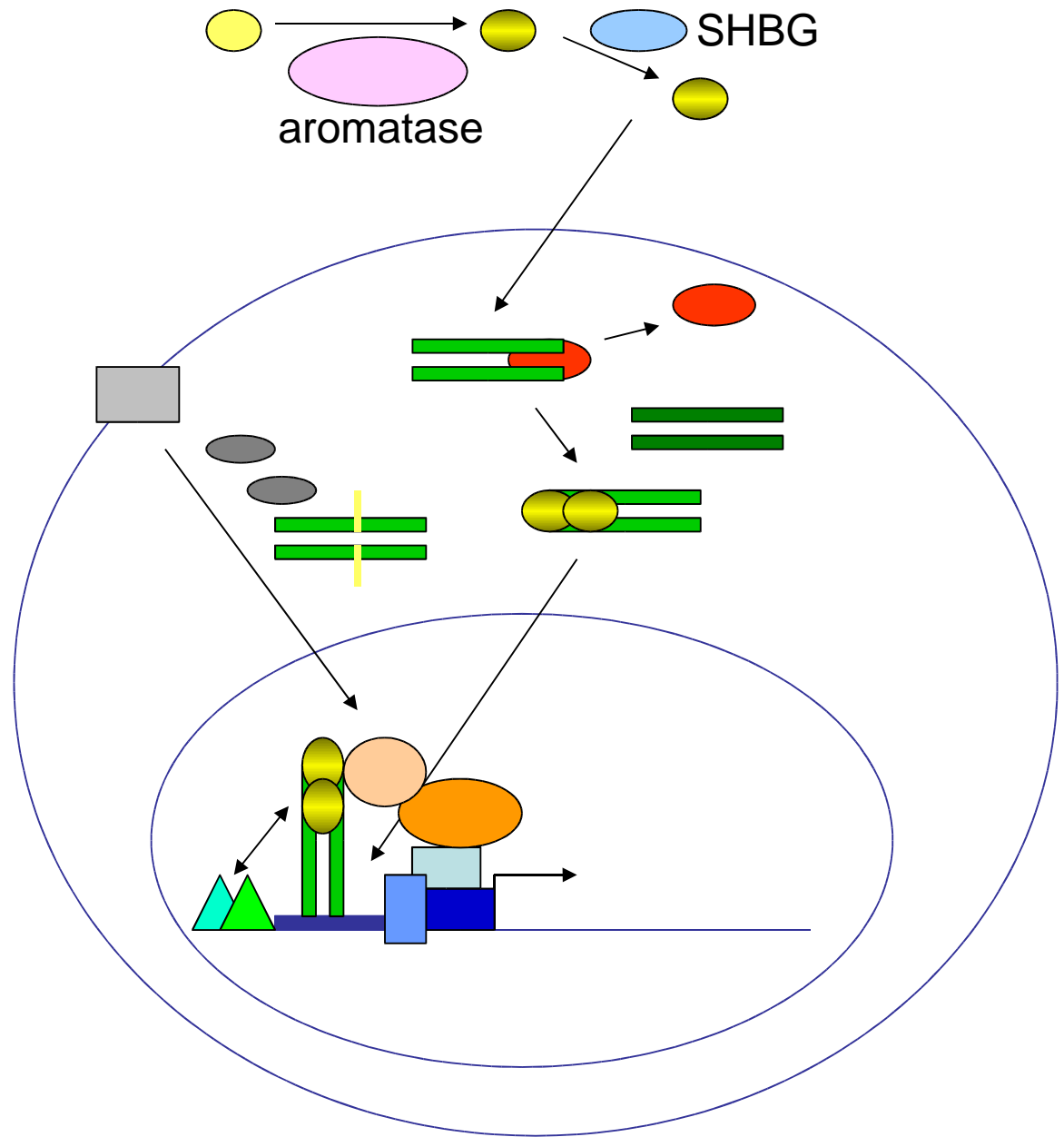


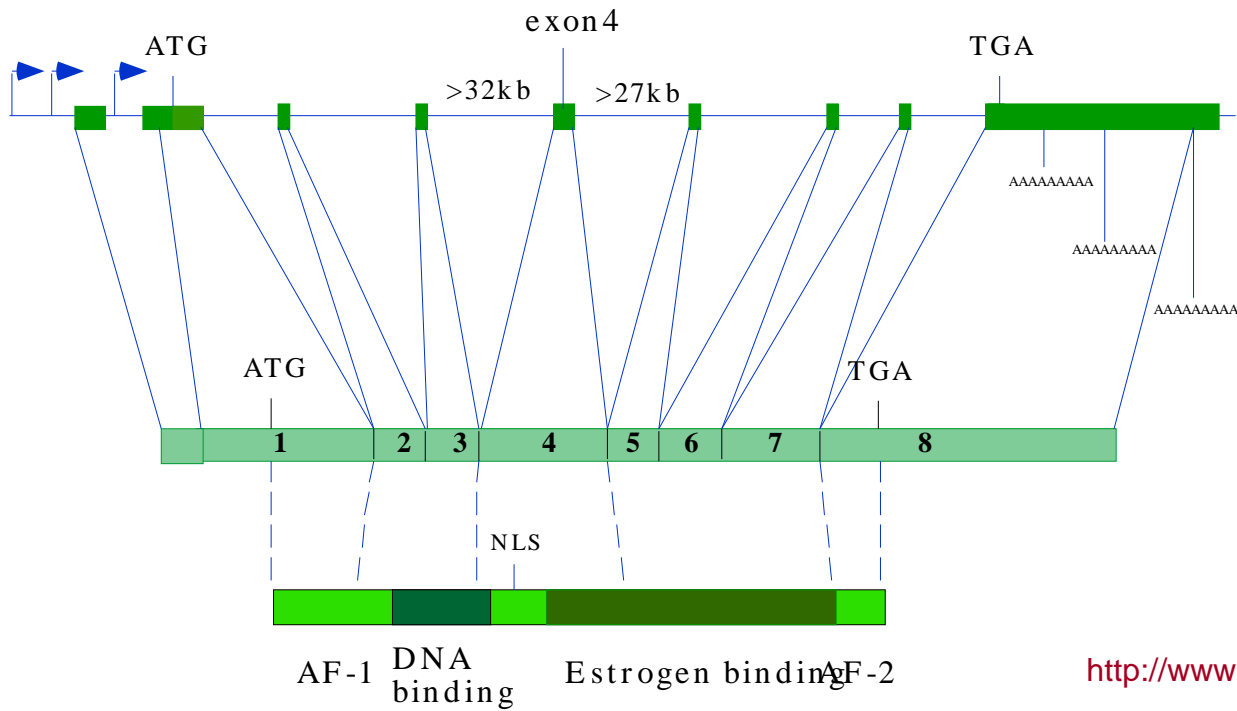








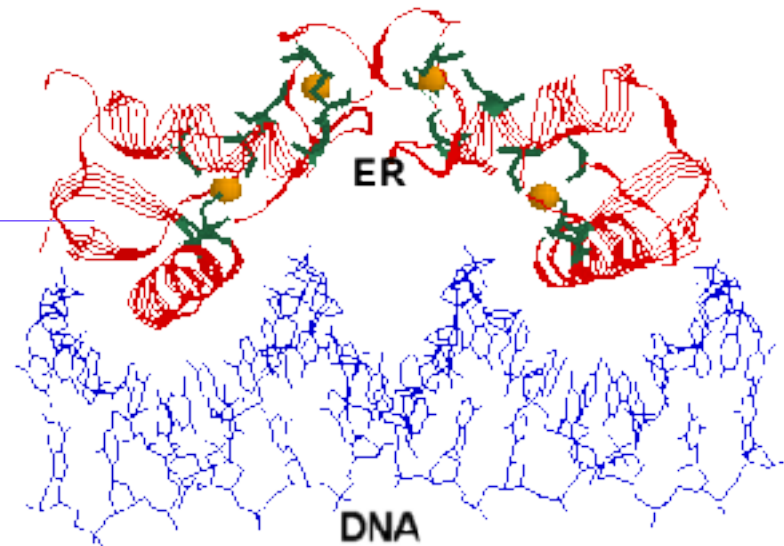




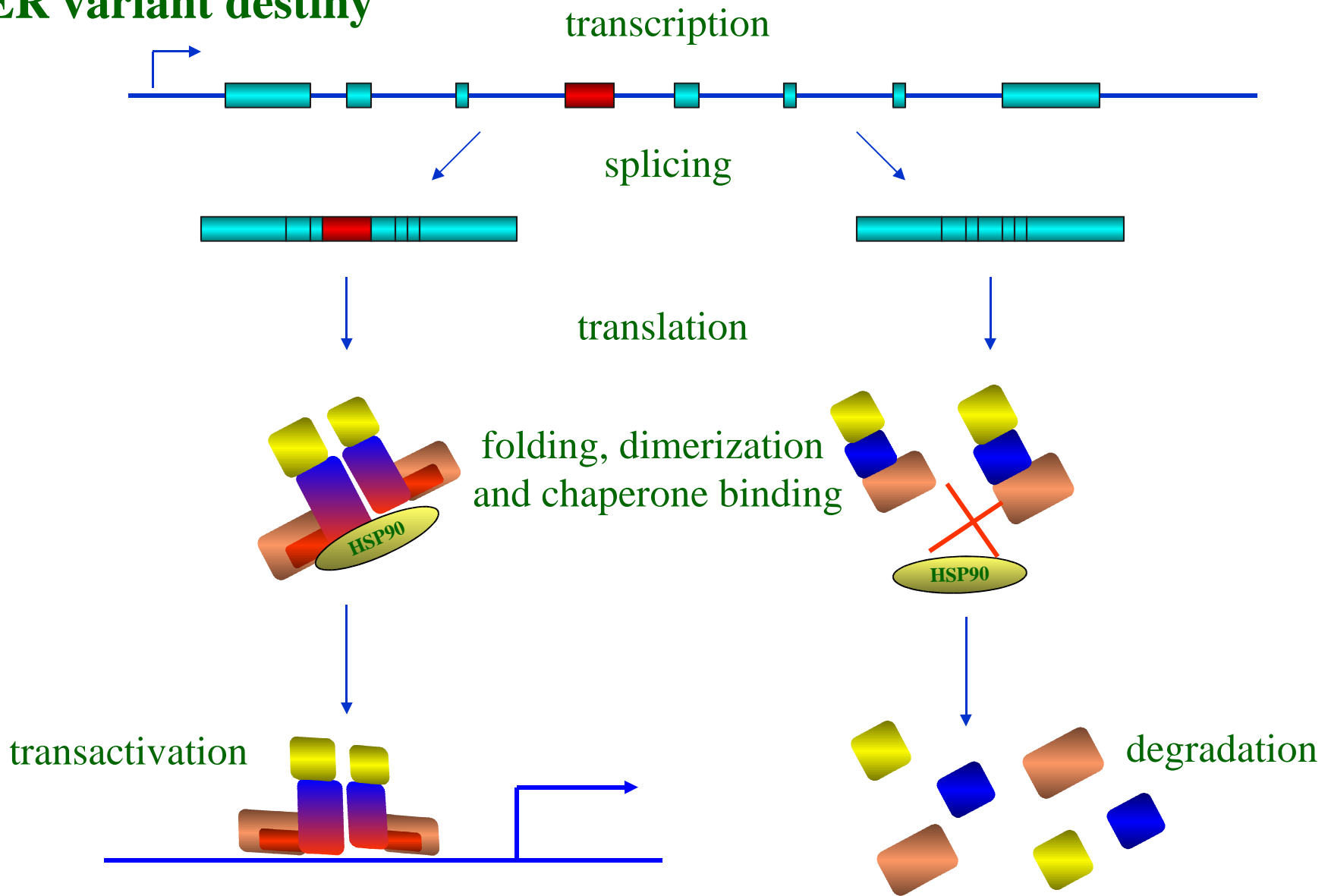
<http://www.web-books.com/MoBio/Free/Ch4F2.htm>

estrogen response element:

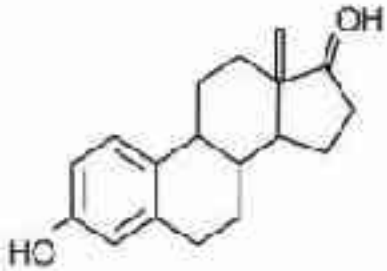
AGAACAnnnTGTTCT
TCTTGTnnnACAAGA



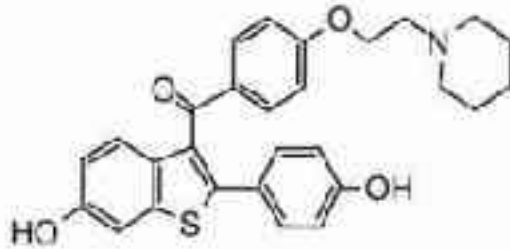
ER variant destiny



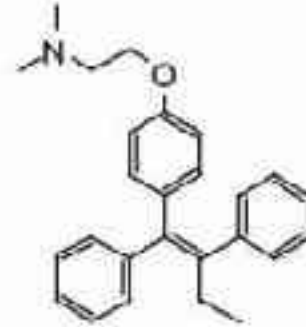
Alternative splicing leads to functional ER or to a variant that is rapidly degraded.
A way to control ER synthesis post-transcriptionally.



Estradiol



Raloxifen



Tamoxifen

Antagonisti parziali - effetti antagonistici ed estrogenici tessuto specifici

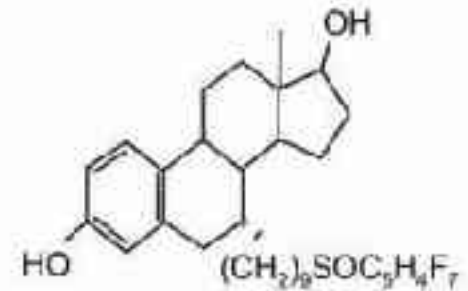
Antagonisti totali

Fitoestrogeni – presenti nella dieta, deboli agonisti metabolizzabili

Xenoestrogeni – contaminanti ambientali, deboli agonisti, effetti

Cumulativi e sinergici

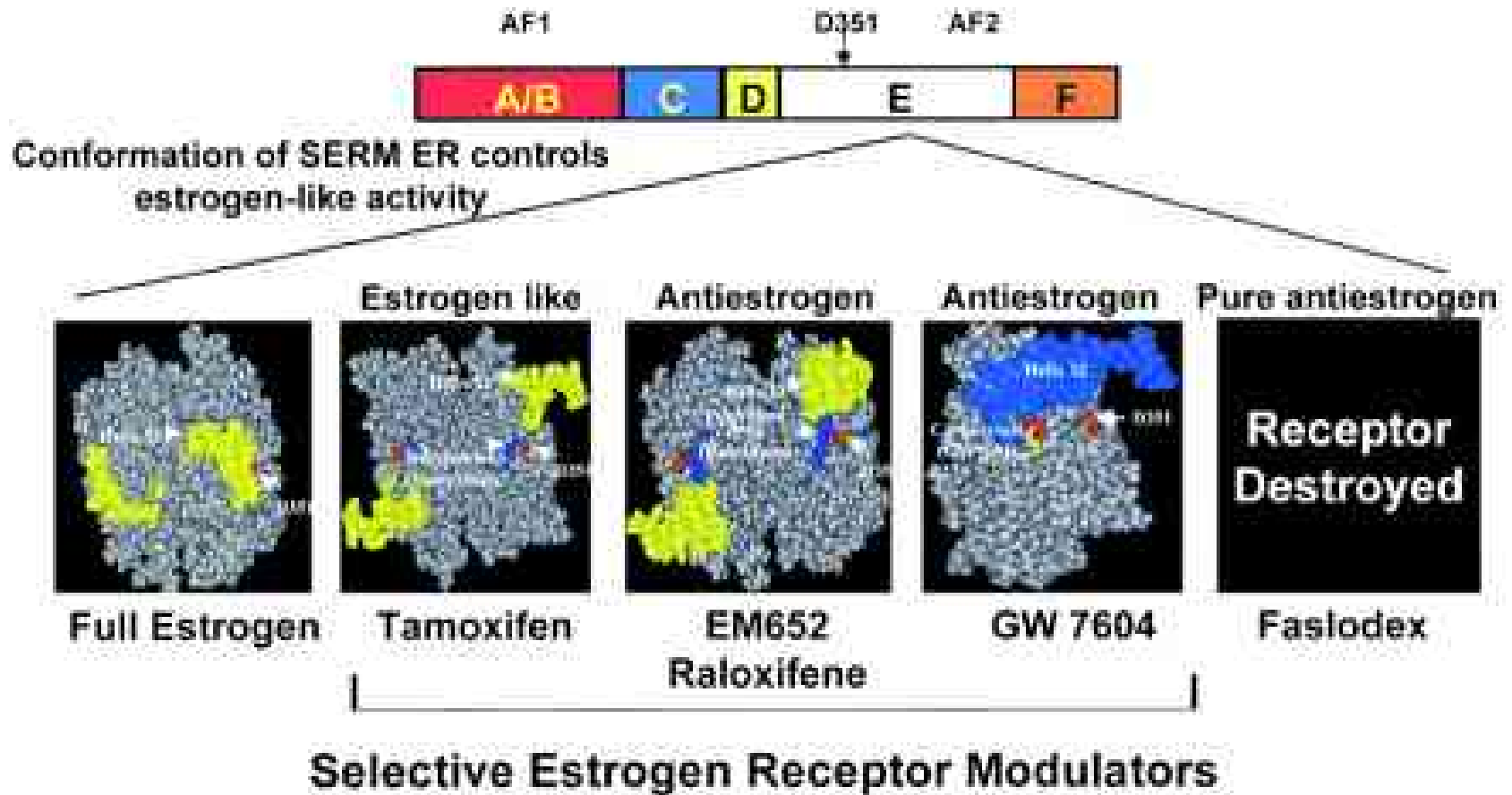
SERM – selective estrogen receptor modifiers, agonisti nel sistema cardiovascolare, osseo e nervoso, antagonisti nella mammella



ICI 182,780

The modulation of the ER complex by interaction of the antiestrogenic side chain of SERMs with surface aminoacid D351

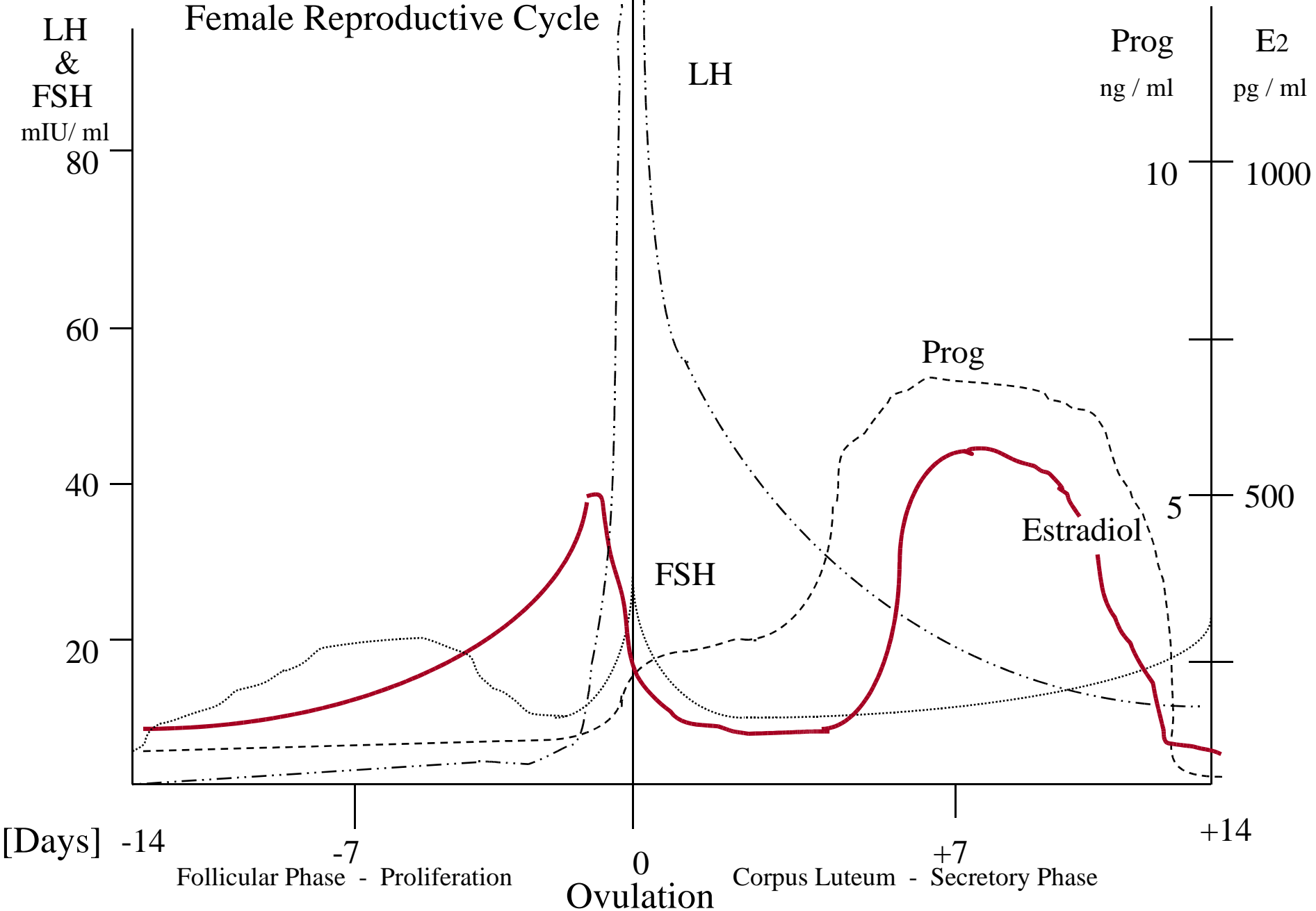
Data adapted from X-ray crystallography and the biology of complexes

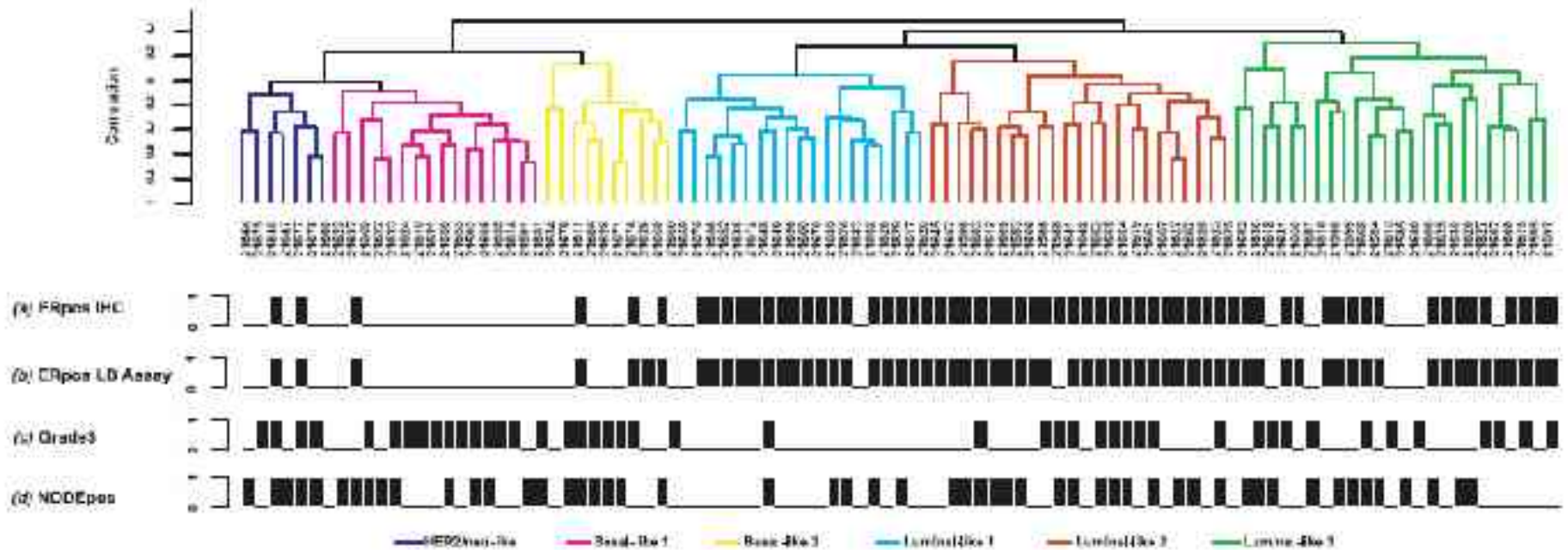


Target Tissues in Females & Males



Female Reproductive Cycle





Christos Sotiriou et al., PNAS, 100, 10393–10398, 2003

Table 2 Prediction of ER status

Genes	Validation		Test	
	Correct ^a	ROC area	Correct ^b	ROC area
Top-100	47	100.00%	11	100.00%
51-150	43	97.80%	9	100.00%
101-200	45	99.30%	11	100.00%
151-250	44	97.50%	9	100.00%
201-300	41	93.70%	11	100.00%
251-350	39	95.30%	9	93.30%
301-400	41	93.10%	8	96.70%
Random	38.8 ± 0.2	91.8 ± 0.2%	5.5 ± 0.2	53.0 ± 2.6%

^a Number of correct classifications of 47 samples.

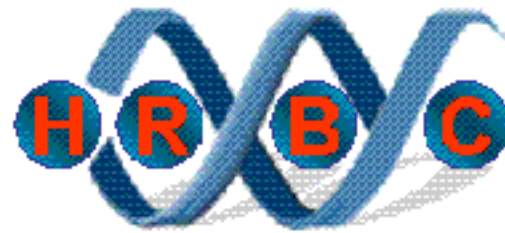
^b Number of correct classifications of 11 samples.

Grubberger et al., CANCER RESEARCH 61, 5979–5984, 2001

What is an estrogen responsive gene?

Identificazione ed analisi funzionale delle alterazioni molecolari e geniche che caratterizzano i tumori della mammella ormono-responsivi

Progetto FIRB, coordinatore: **Alessandro Weisz**, Napoli



Hormone Responsive Breast Cancer Genomics Network

<http://www.hrbc-genomics.net>