City of Hope

Cancer Genetics and the Prospects for Cancer Therapeutics

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HBA-USA Conference

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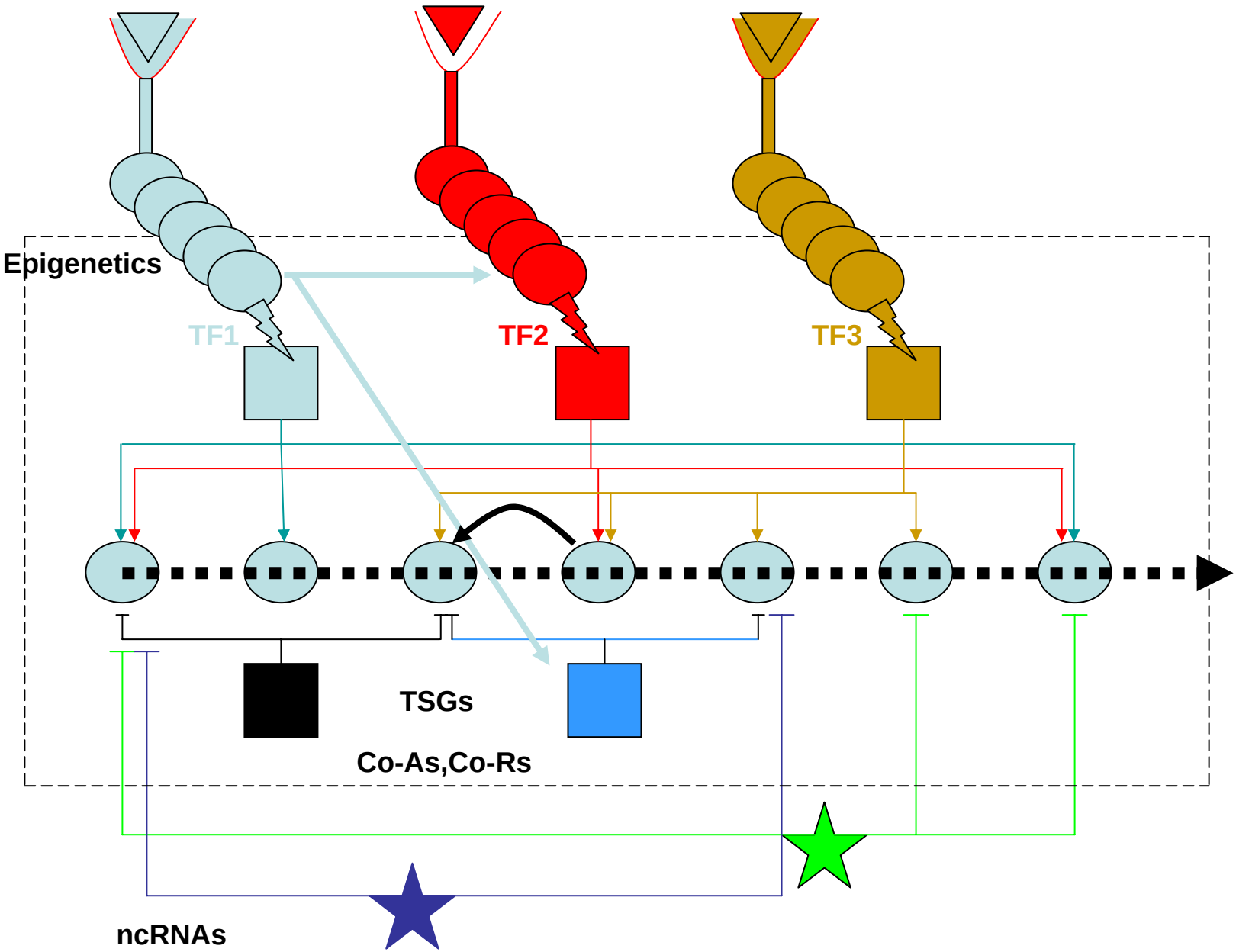
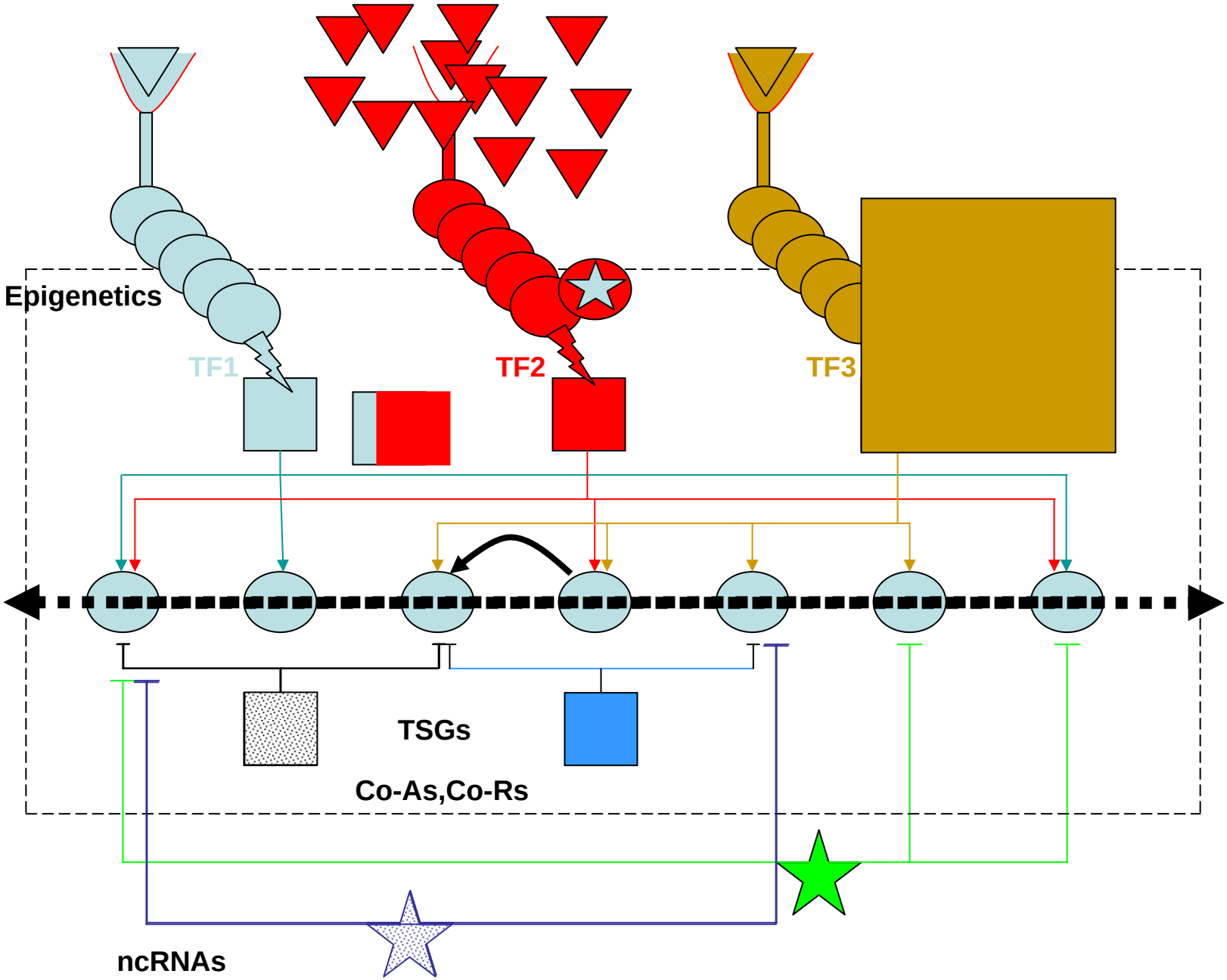

Epigenetics
TF1
TF2
TF3
TSGs
Co-As,Co-Rs
ncRNAs

1. To integrate multiples inputs across multiple cooperating entities (genes) to produce a coherent, reproducible output (phenotype)
2. To resist disruption; to serve as the mechanism of homeostasis—that is, to keep that phenotype *stable*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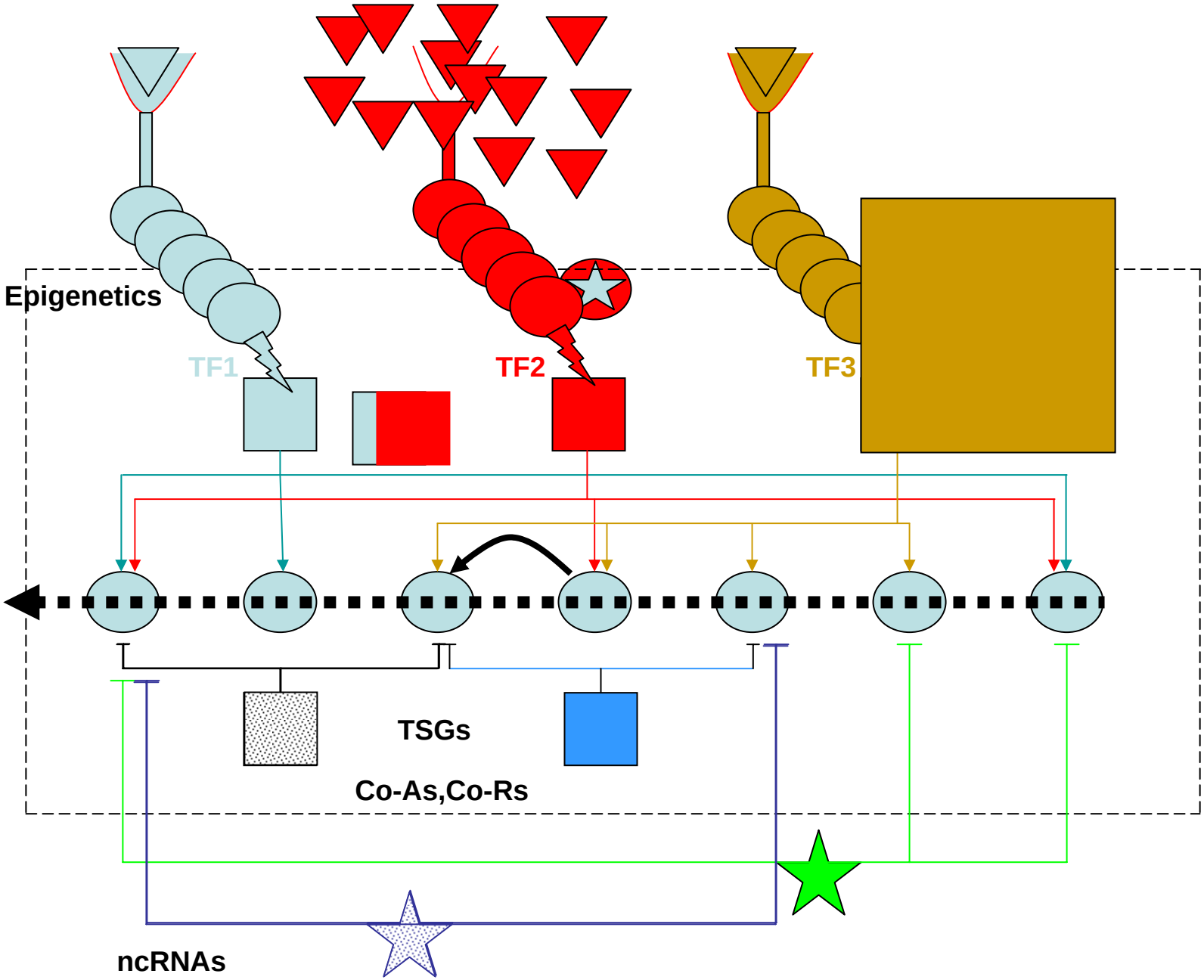
How many lesions are enough?

Weinberg data—4 to 6 genes

Deep sequencing data—over
60 mutated genes, affecting
at least 12 *known* pathways

Why the discrepancy?
Tumor (cell) heterogeneity
New organ, hell-bent on homeostasis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Successes: imatinib (Gleevec)

erlotinib (Tarceva), sorafenib (Nexavar), sunitinib (Sutent),…

Failures: many, many

Validate target

Screen for small molecule modulator

Pre-clinical tox studies; "drugability"/formulation

Phase I, II trials:
PK, PD, toxicity, efficacy

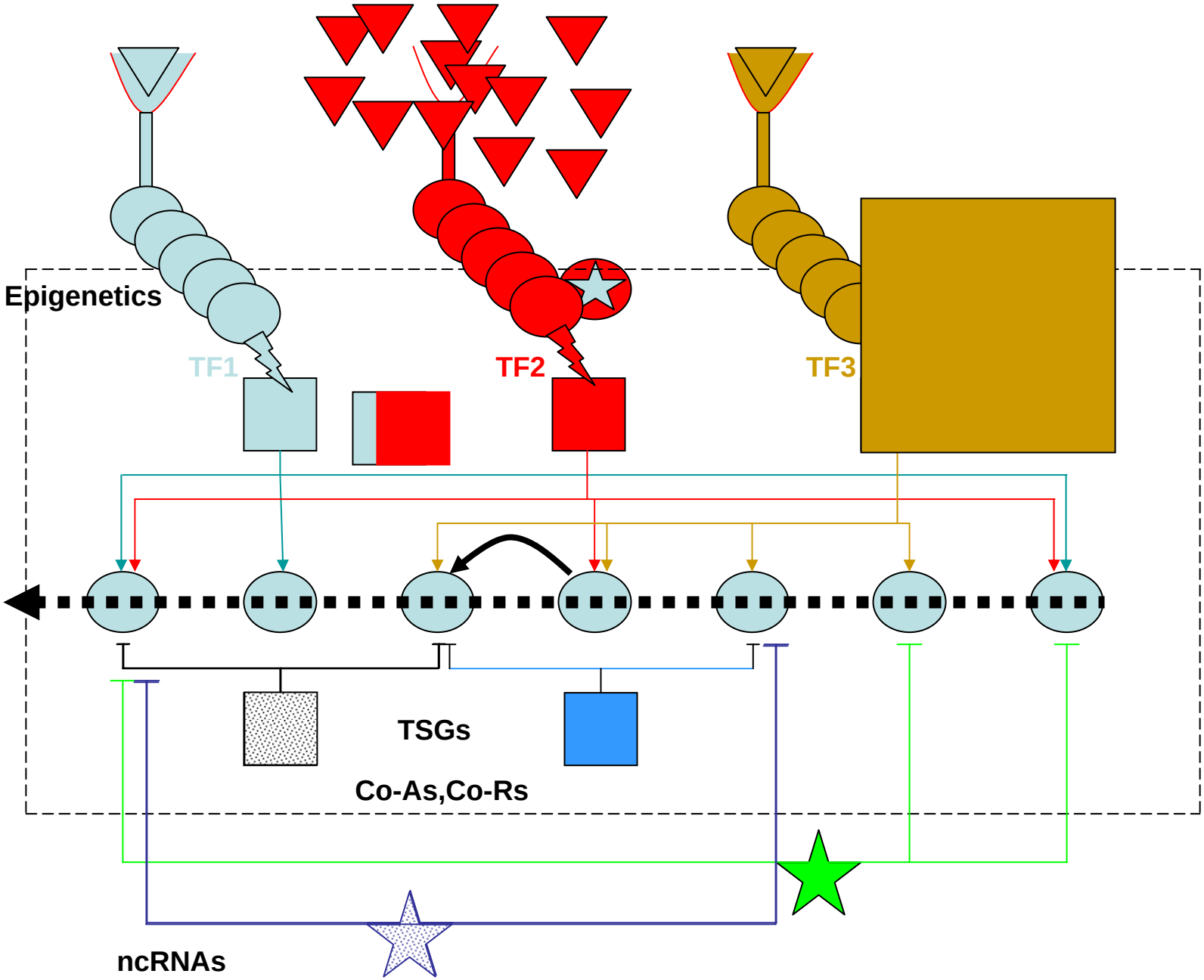
Ideal combination cancer therapy of the past:

Non-overlapping targets
Non-overlapping toxicities
Non-overlapping mechanisms of resistance

Ideal combination cancer therapy for the future:

Interdependent targets

- "oncogene/pathway addiction"
- "synthetic lethality"
- interdicted by-pass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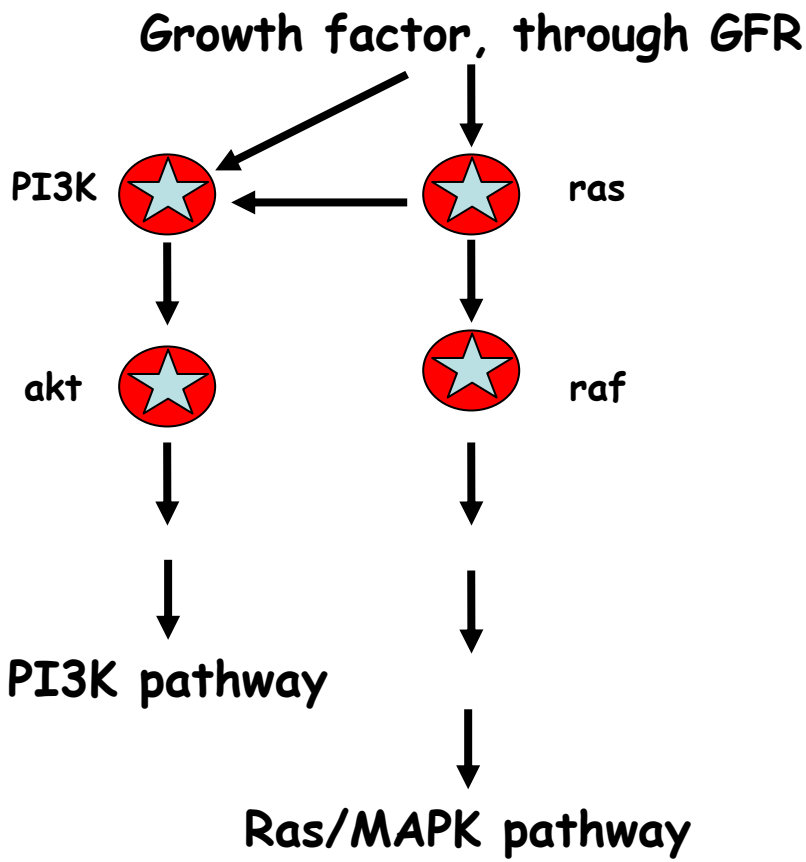
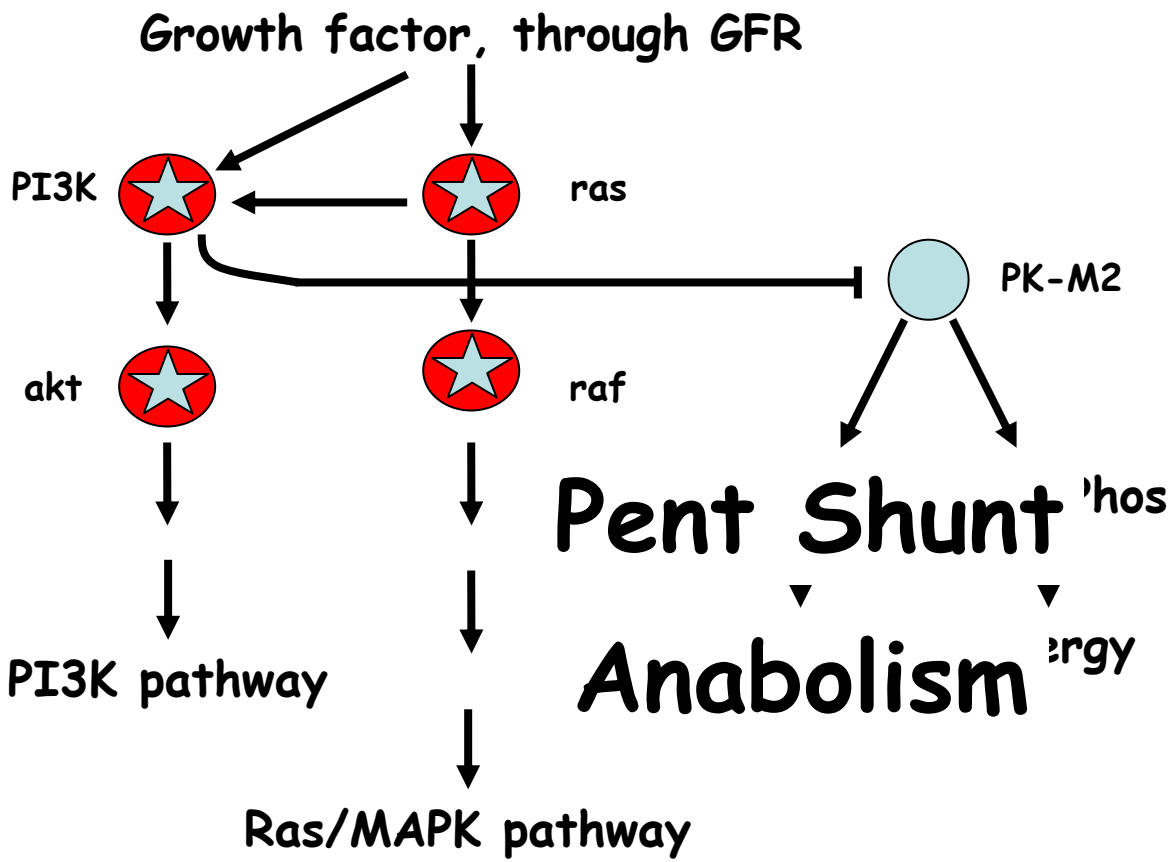

Growth factor, through GFR
PI3K
ras
akt
raf
PI3K pathway
Ras/MAPK pathway

Ideal combination cancer therapy for the future:

Interdependent targets

- "oncogene/pathway" addiction
- "synthetic lethality"
- interdicted by-pass
- exploitation of cancer metabolism



Cantley/Rosen
Tsichlis

Ideal combination cancer therapy for the future:

Interdependent targets
- "oncogene/pathway" addiction
- "synthetic lethality"
- interdicted by-pass
- exploitation of cancer metabolism
- cues to the microenvironment

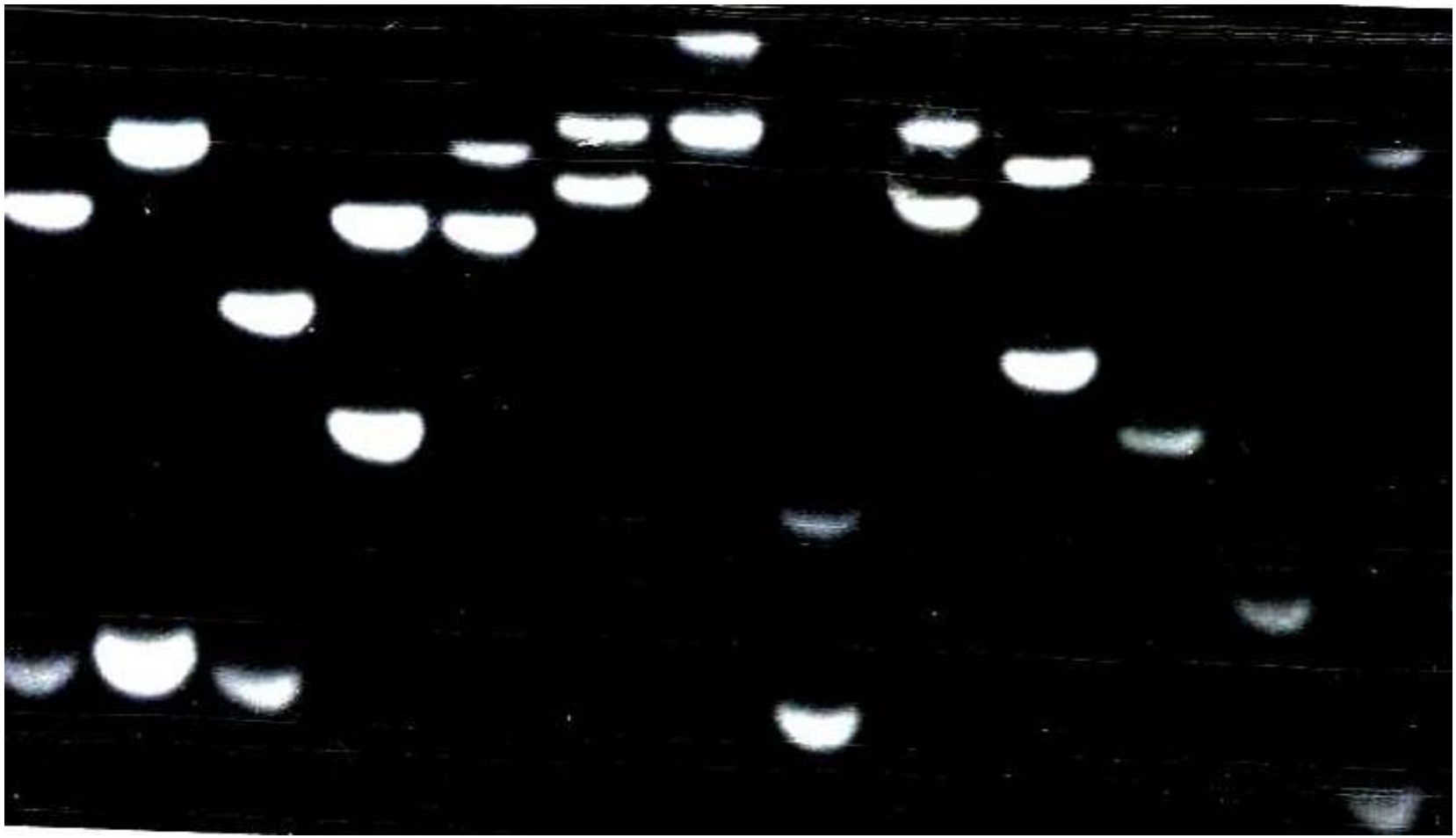
Defined patient responder subset

Parting message:

The wiring diagram of the therapy has to be at least as complex as the wiring diagram of the disease state.

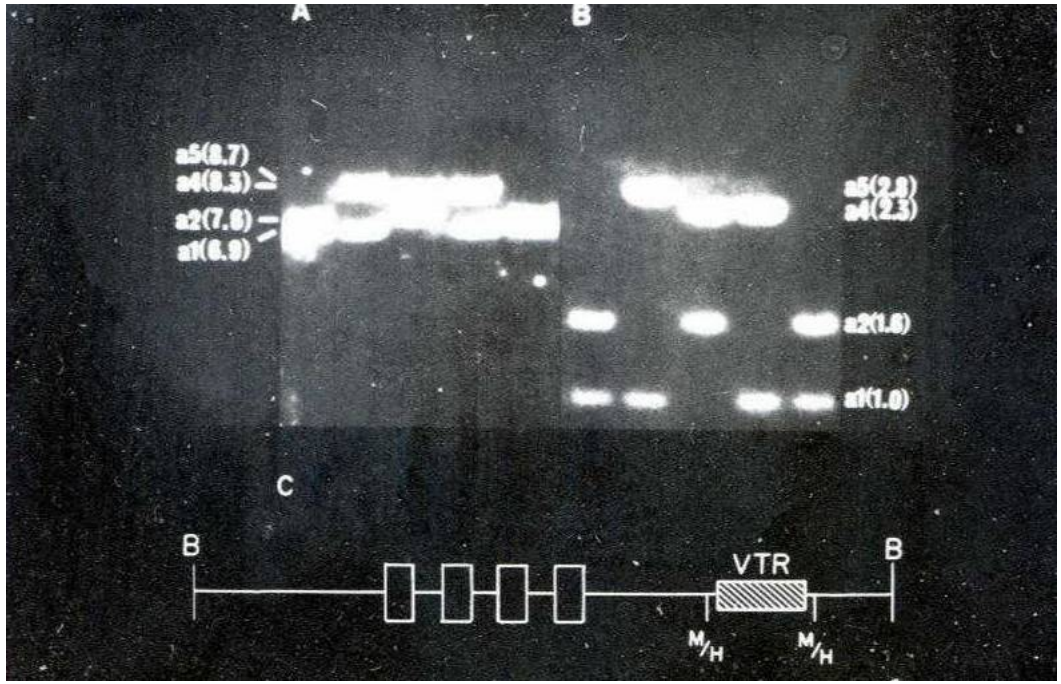
City of Hope

Human Minisatellites and Human Disease



5′-CCAGGGGACGCCACACTCXCCCTTCTXT-3′

28 bp consensus sequence of the human *HRAS* minisatellite


A
B
a5(8.7)
a4(8.3)
a2(7.8)
a1(6.9)
a5(2.8)
a4(2.3)
a2(1.8)
a1(1.0)
C
B
VTR
B
M/H
M/H

The *HRAS* Minisatellite—initial considerations

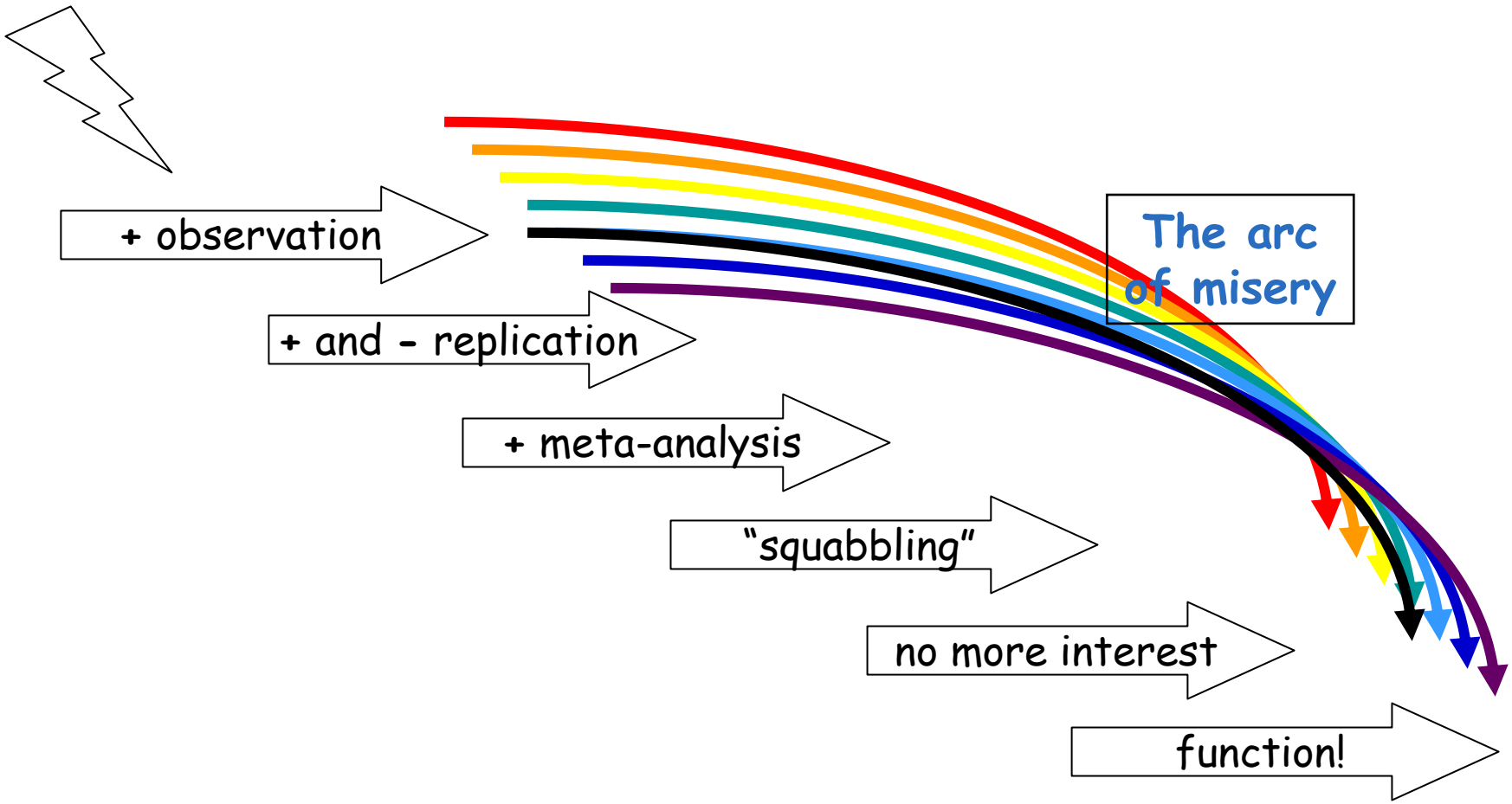
- Can such an unstable region, located 1500 bp from the (then known) polyadenylation signal of the proto-oncogene, *HRAS*, influence cancer risk?

Cancer Association and the *HRAS* Minisatellite

	a1	a2	a3	a4	rare	n	P value
Original study*							
Cases	.62	.11	.07	.08	.12	164	0.005
Controls	.69	.12	.11	.06	.04	230	
Follow-up+							
Cases	.60	.11	.11	.07	.12	736	0.002
Controls	.60	.12	.11	.10	.07	652	
Both studies							
Cases	.60	.11	.10	.07	.12	900	<0.001
Controls	.62	.12	.11	.09	.06	882	

* *Nature*, 1985
\+ *NEJM*, 1993

The natural history of an observation from genetic epidemiology of a positive disease association



The *HRAS* Minisatellite—current considerations

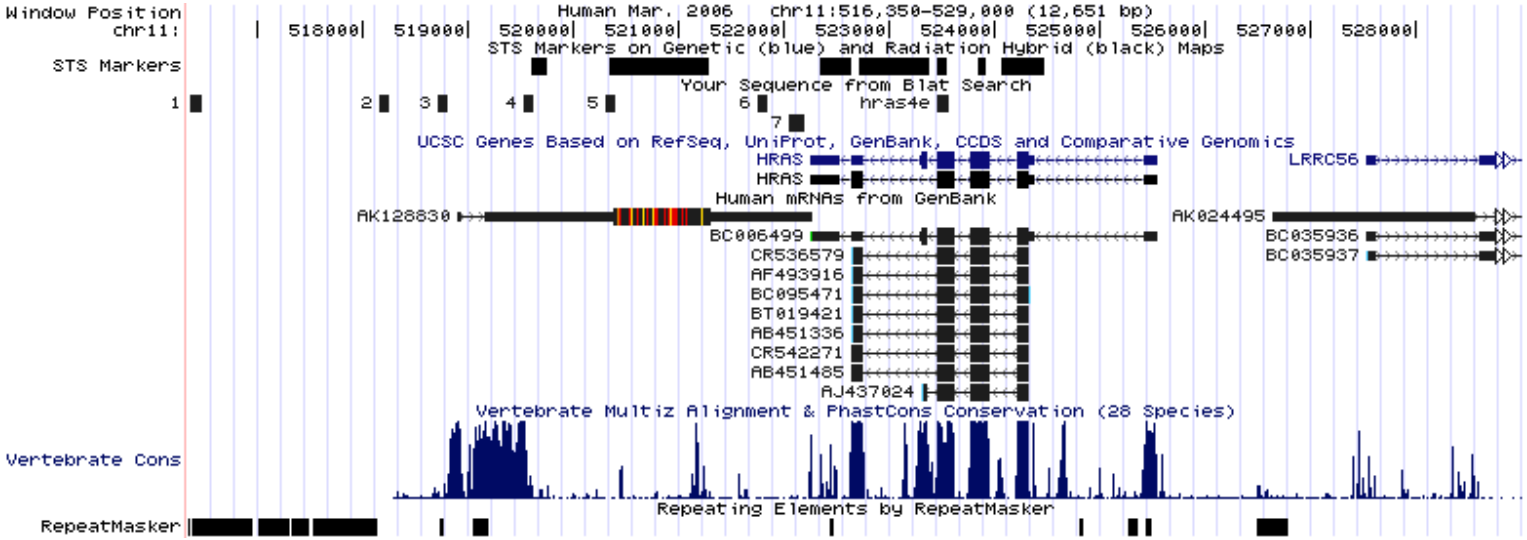
- Can such an unstable region, located 1500 bp from the (then known) polyadenylation signal of the proto-oncogene, *HRAS*, influence cancer risk?

- Can there be intrinsic functional properties of such an unstable region?

HRAS Minisatellite F[illegible]?

- Against:
  - Instability
  - Only appears in higher primates
  - Monotonous, though open, reading frame
- For?
  - Detected on an independent, capped, spliced, polyadenylated RNA transcript

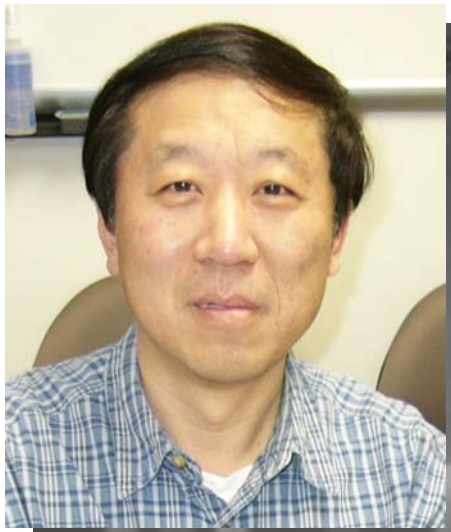
Expression (RTPCR) across the *HRAS* VNTR-containing LD Block



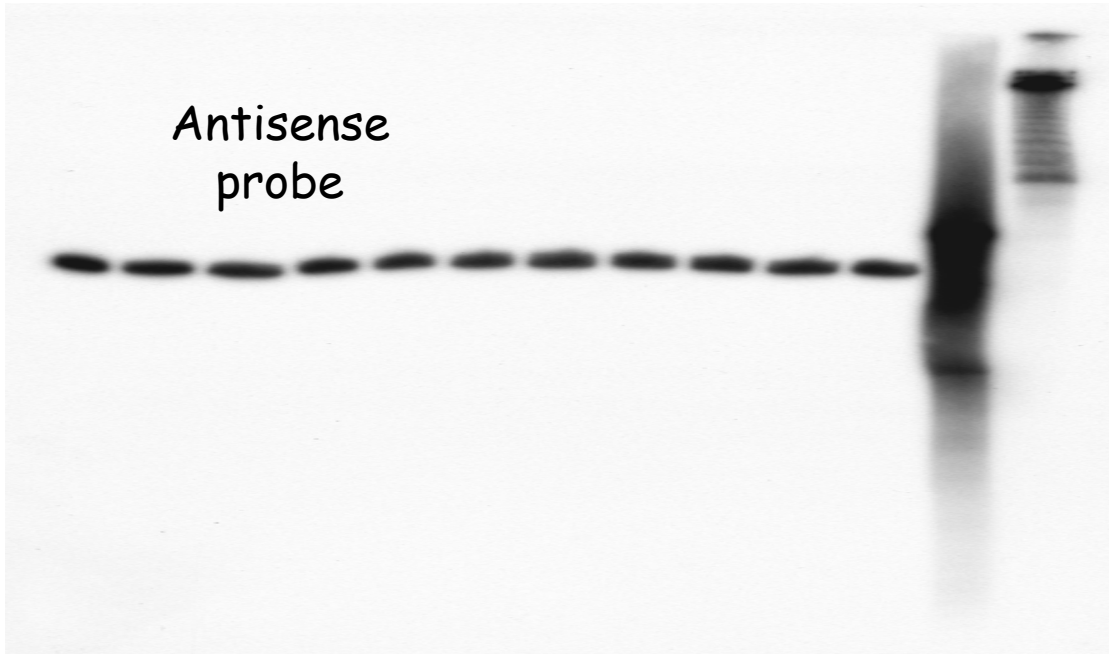
Testes hexamer-synthesized cDNA
Three 100-bp amplicons in ENCODE transcriptionally silent regions (chr16)
Eight 100-bp amplicons across the *HRAS* LD block (chr11)

-- : no template
G: 10 ng genomic DNA
R: 10 ng total RNA (-RT)
C: 10 ng cDNA

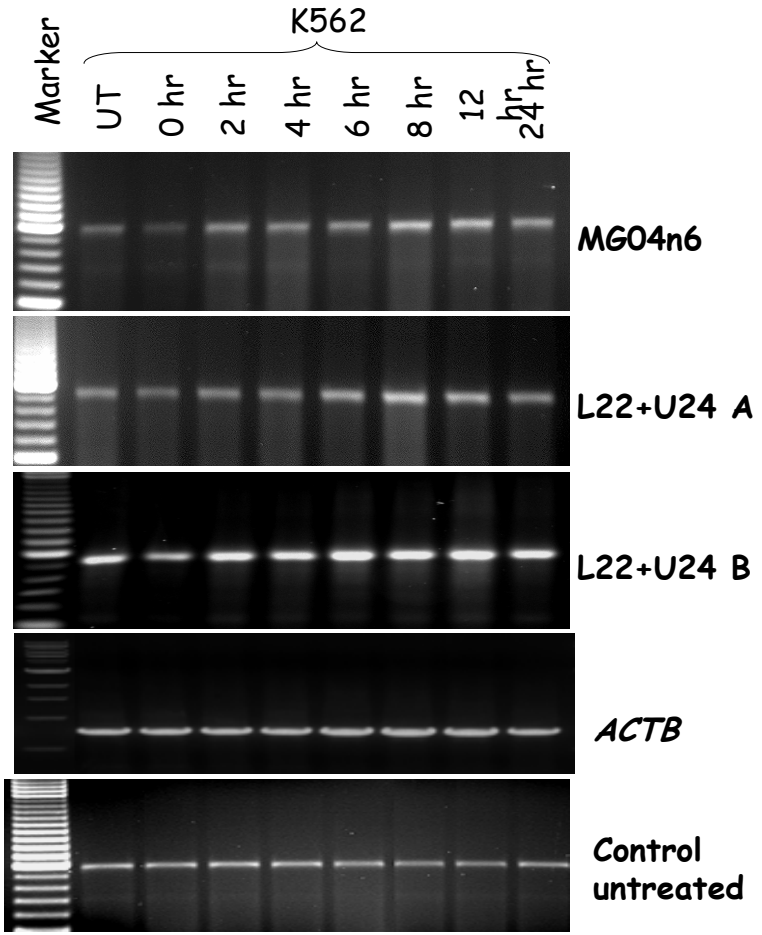
Figure 5A

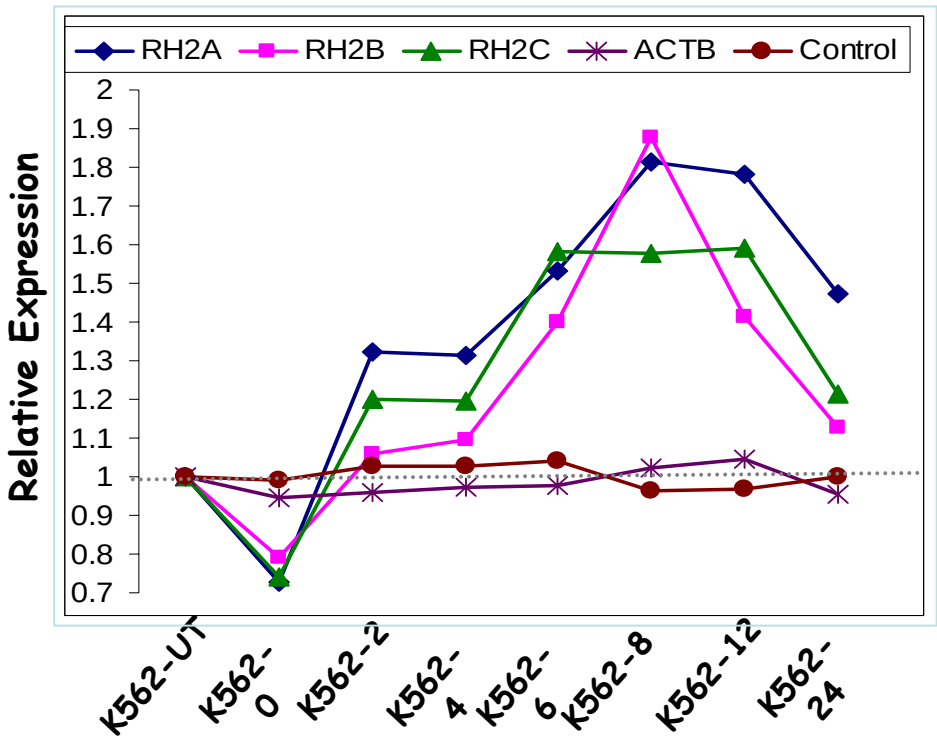


No RT
Random priming
Antisense
Sense
No RT
Random priming
Antisense
Sense

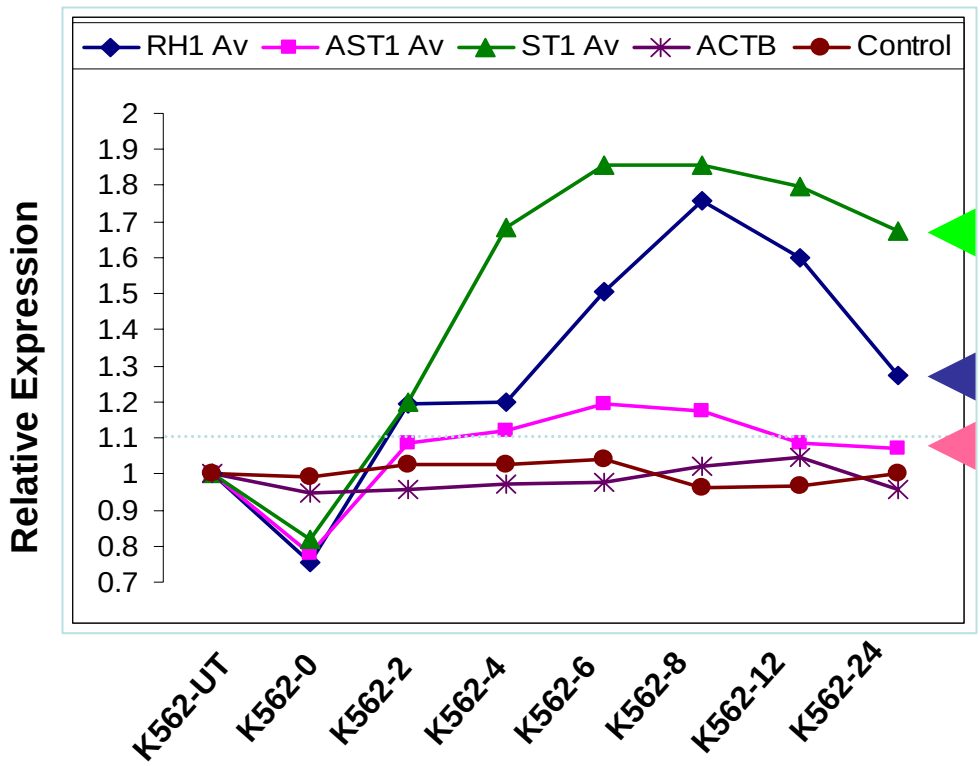

Antisense
probe
971 bp
803 bp
663 bp
112 bp
56 bp

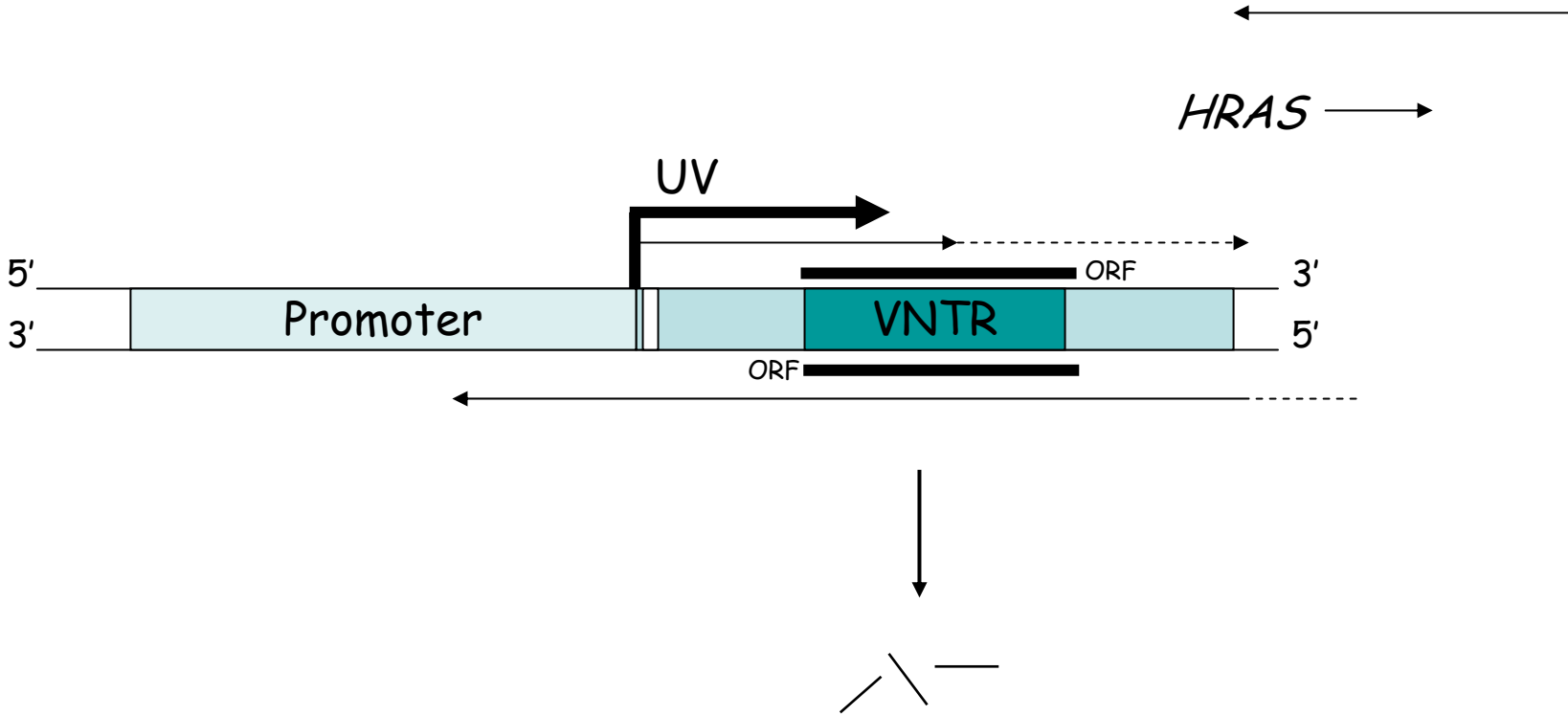
Relative transcription of HRAS-VNTR in control K562 cells & after UV treatment





UV radiation & HRAS-VNTR transcripts




HRAS
UV
5′
3′
Promoter
VNTR
ORF
3′
5′
ORF