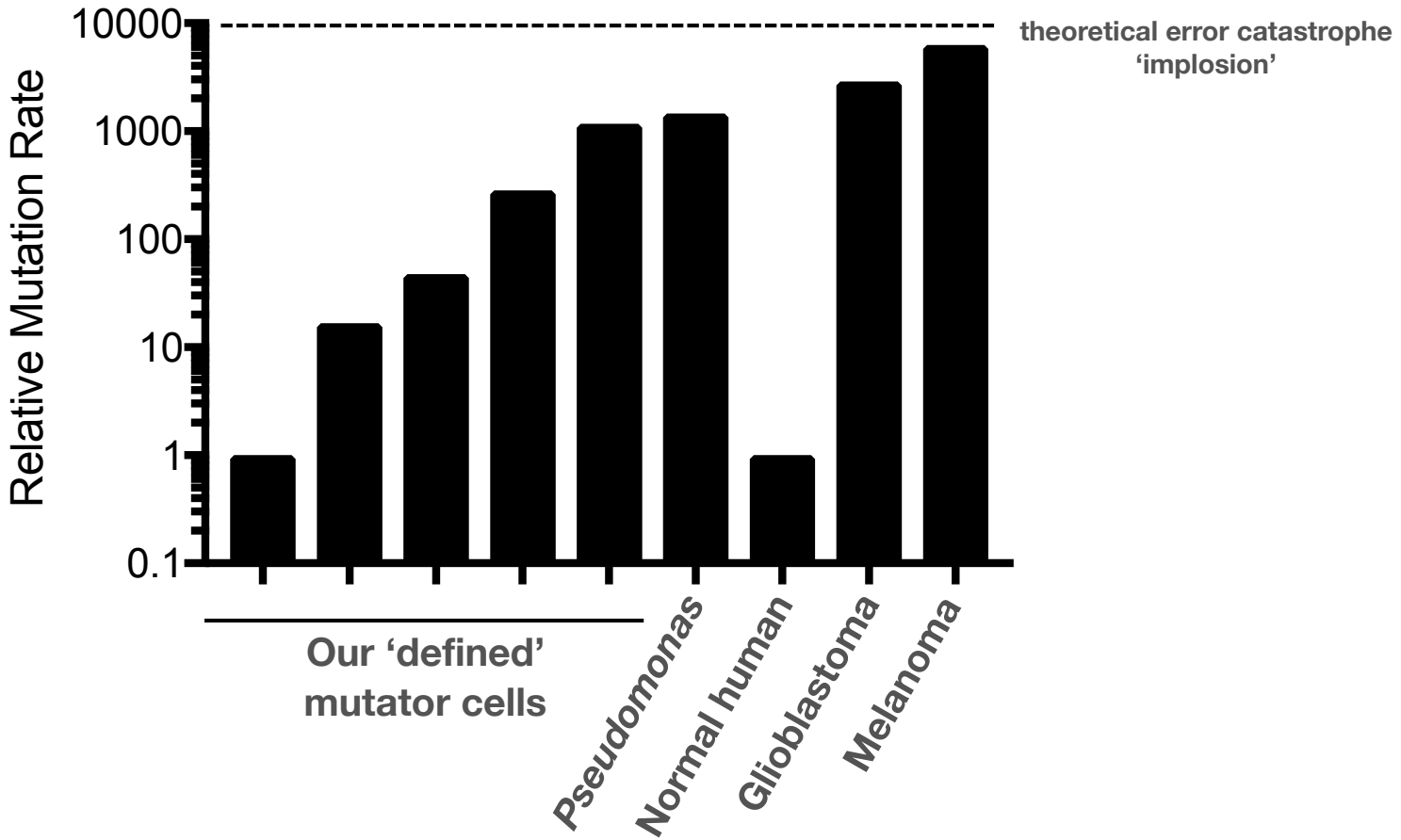
Cancers accumulate an extraordinary number of mutations — verging on error catastrophe



Yet they are evolutionary masters

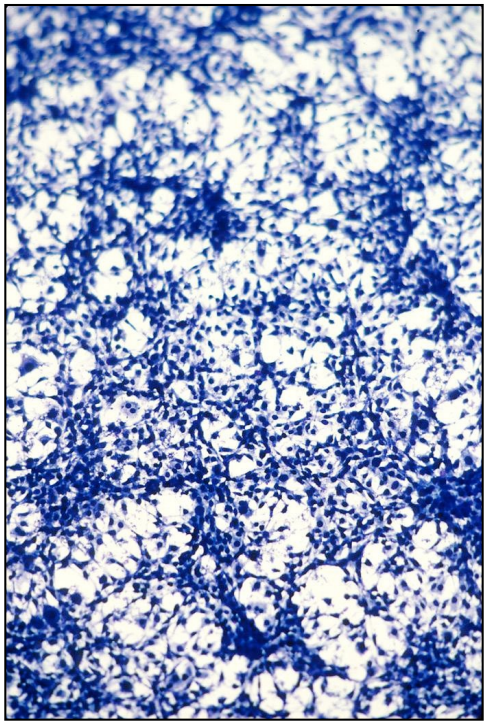
They *limit* the cost of mutations and simultaneously *harness* their potential to evolve drug resistance

This property is part of why drugging these systems is difficult

But does it also create vulnerabilities?

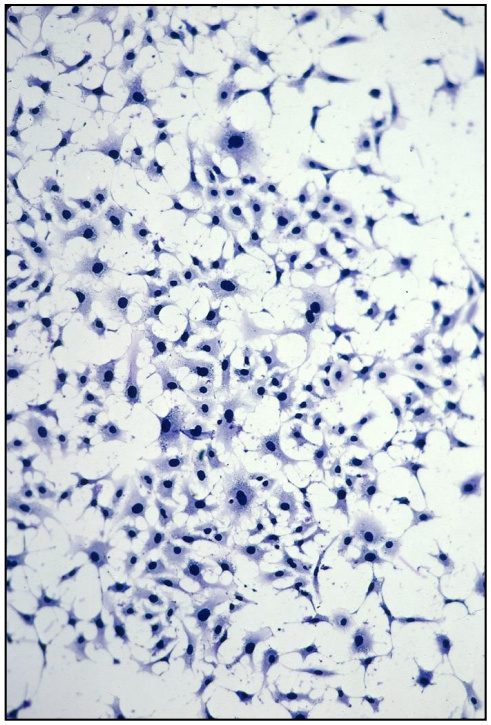
This property depends on specific genes

ONCOGENE CAUSES CANCER



v-Src

ONCOGENE DOES NOTHING

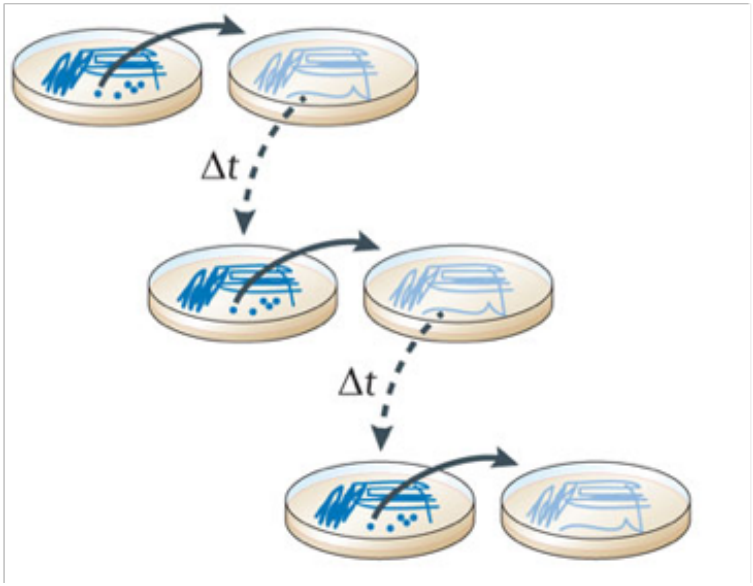


v-Src +
HSP90 INHIBITOR

Would targeting these '*Achilles heels*' have potential as a therapeutic strategy?

Inhibiting Hsp90 is very toxic. Can we identify other Achilles' heels that might be better drug targets?

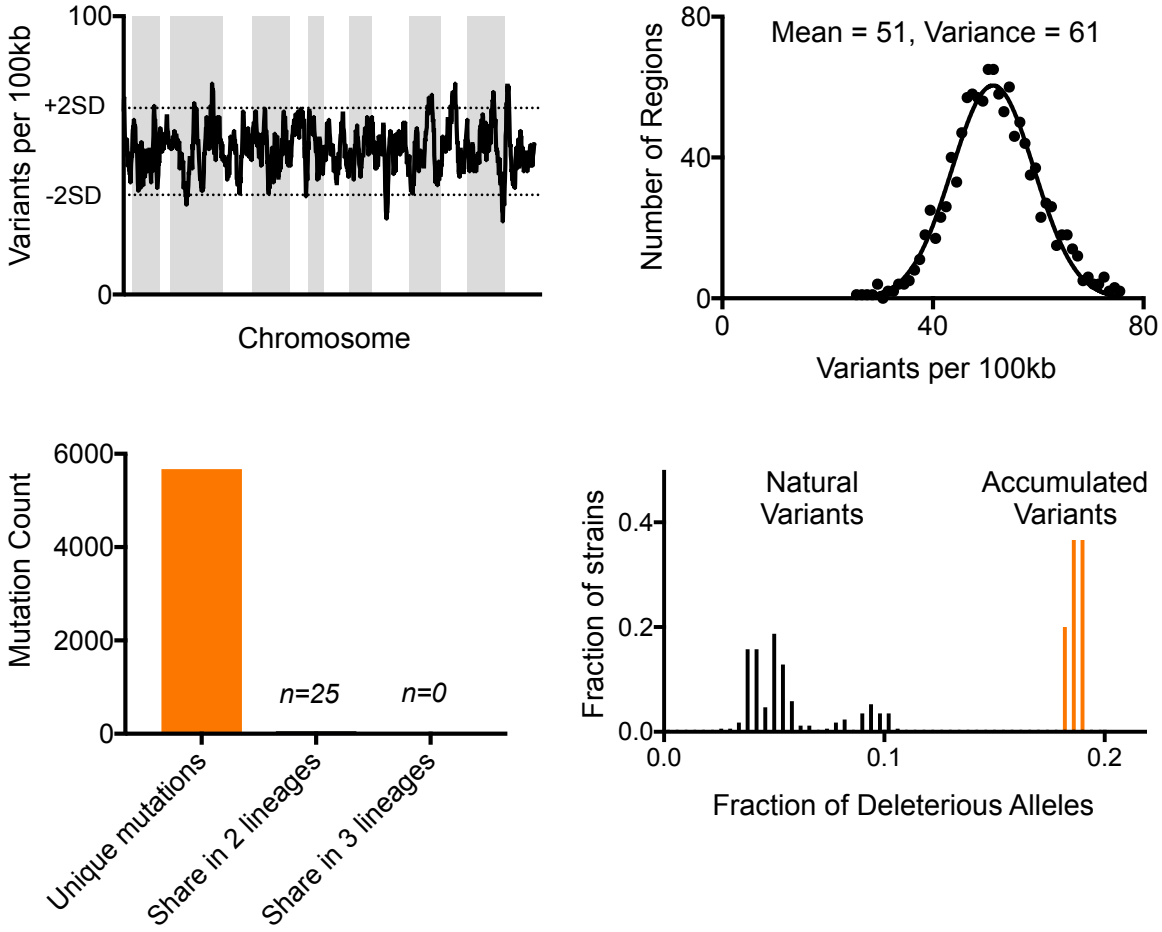
Mutation accumulation



Use cells with high mutation rates - mimic MMR defects in CRC

Watch what happens to fitness as they accumulate mutations

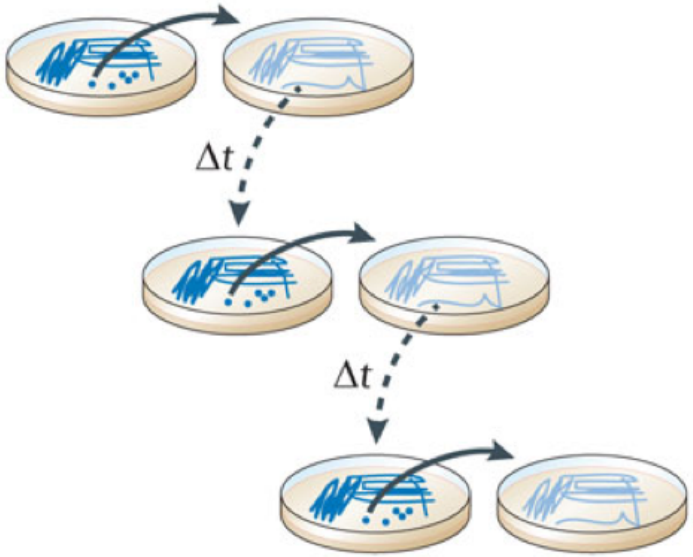
Mutations occur as ‘randomly’ as possible

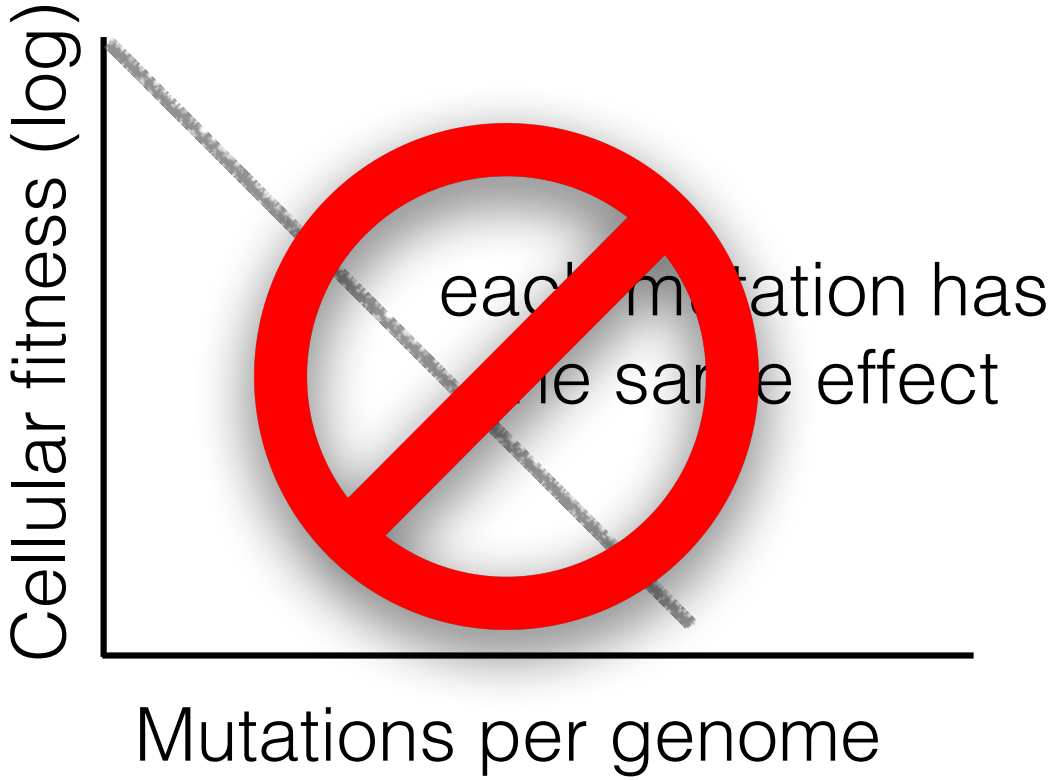


Mutator phenotype is maintained

Highly mutating cells ‘buffer’ the cost of mutations

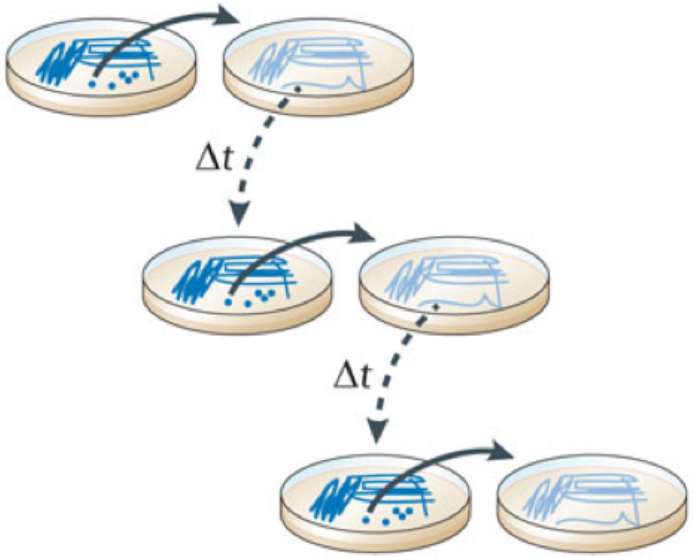
Mutation accumulation

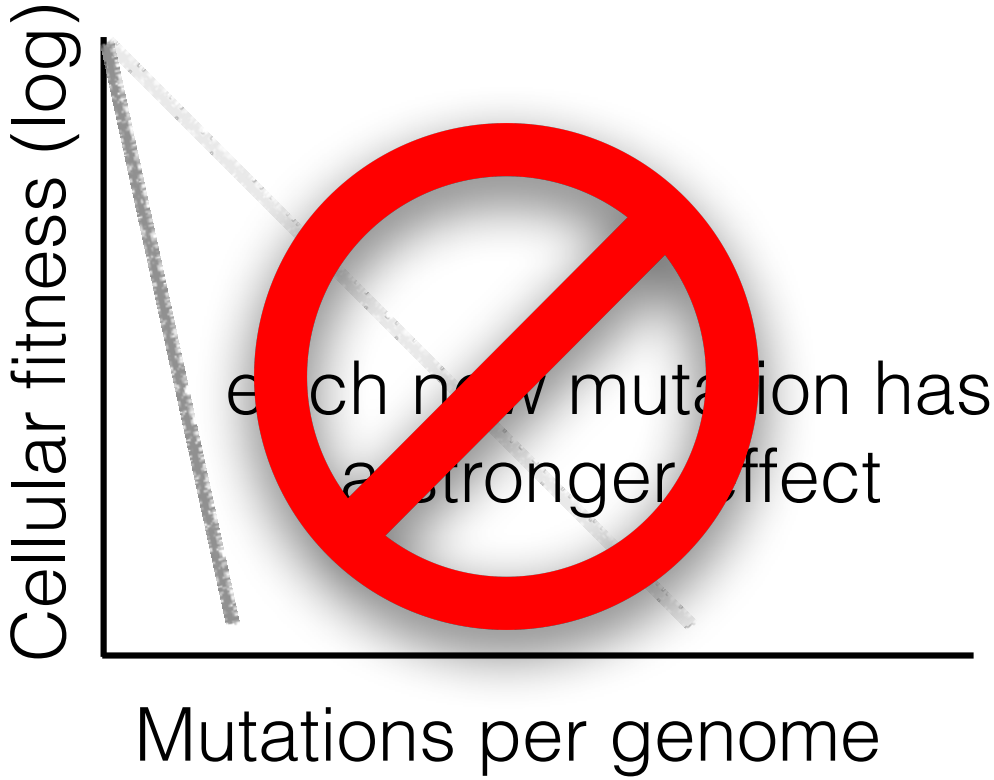




Highly mutating cells ‘buffer’ the cost of mutations

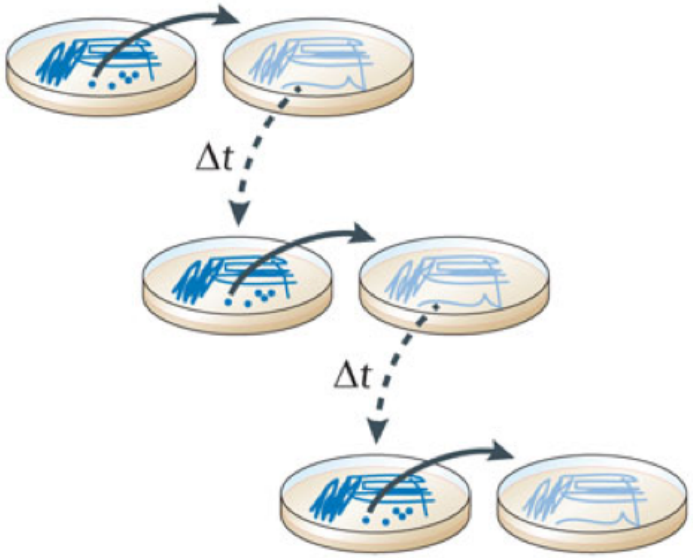
Mutation accumulation

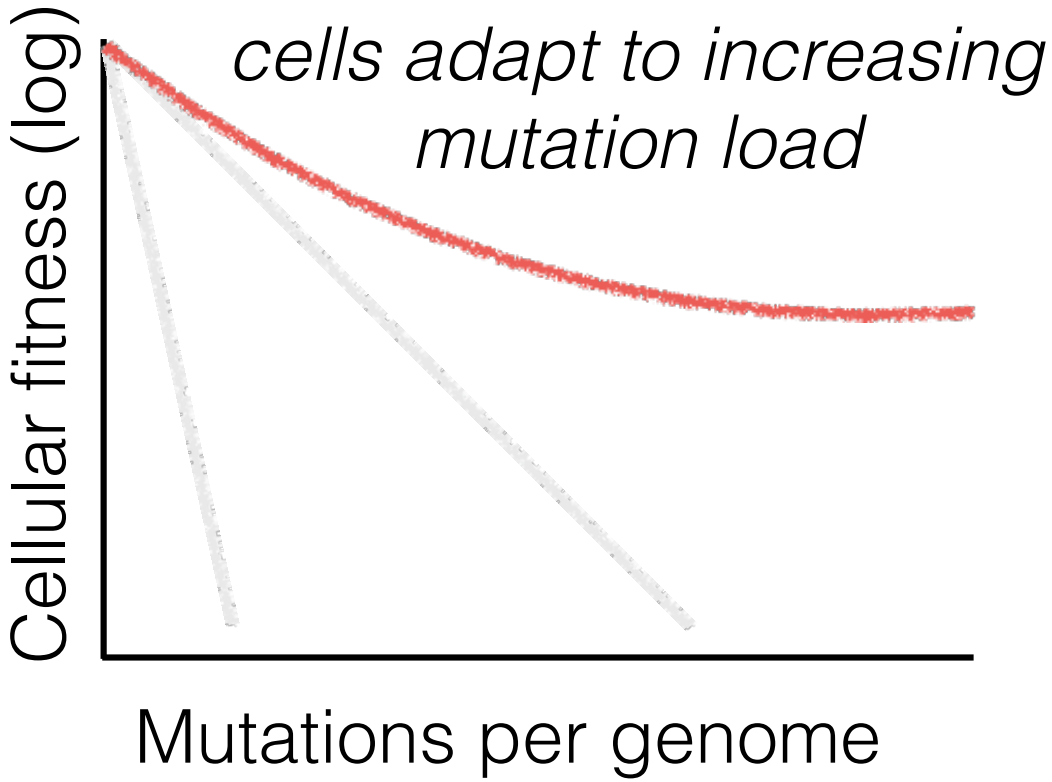


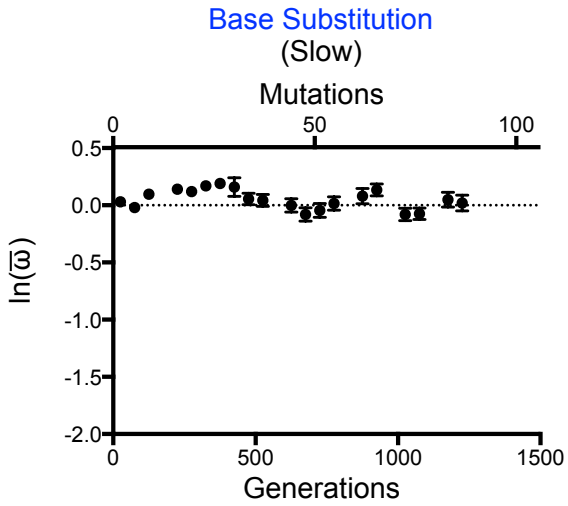


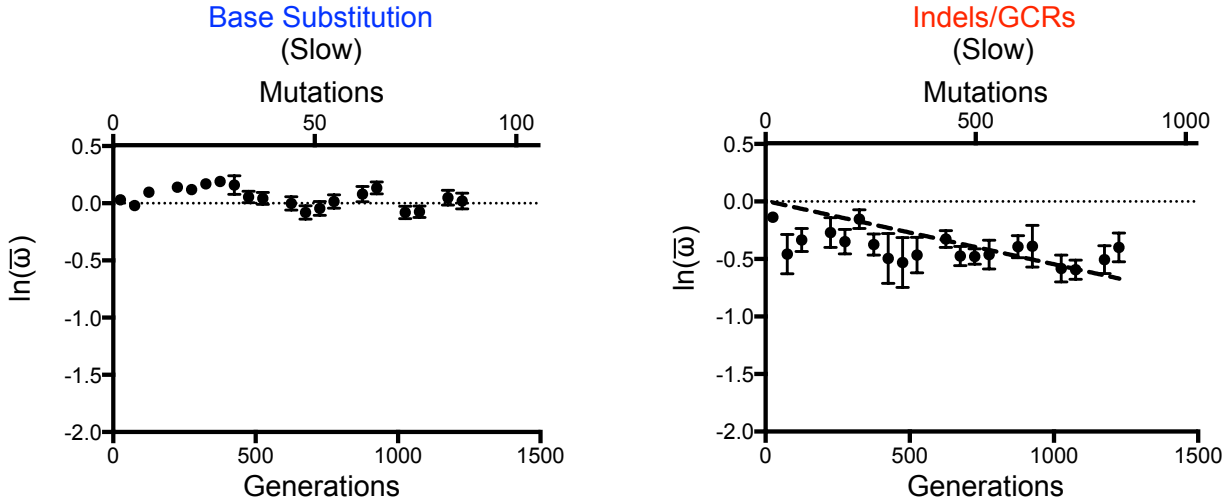
Highly mutating cells ‘buffer’ the cost of mutations

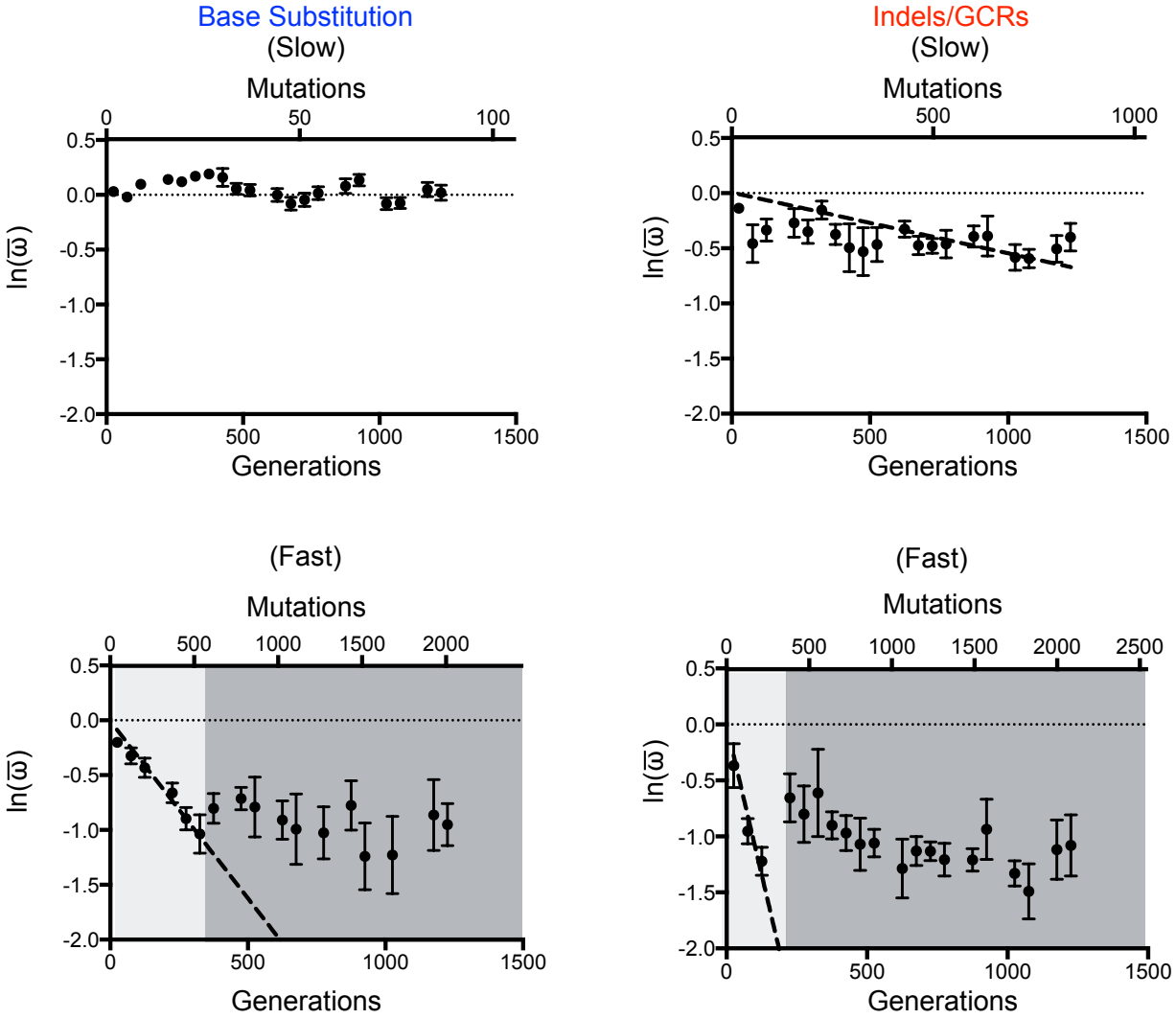
Mutation accumulation

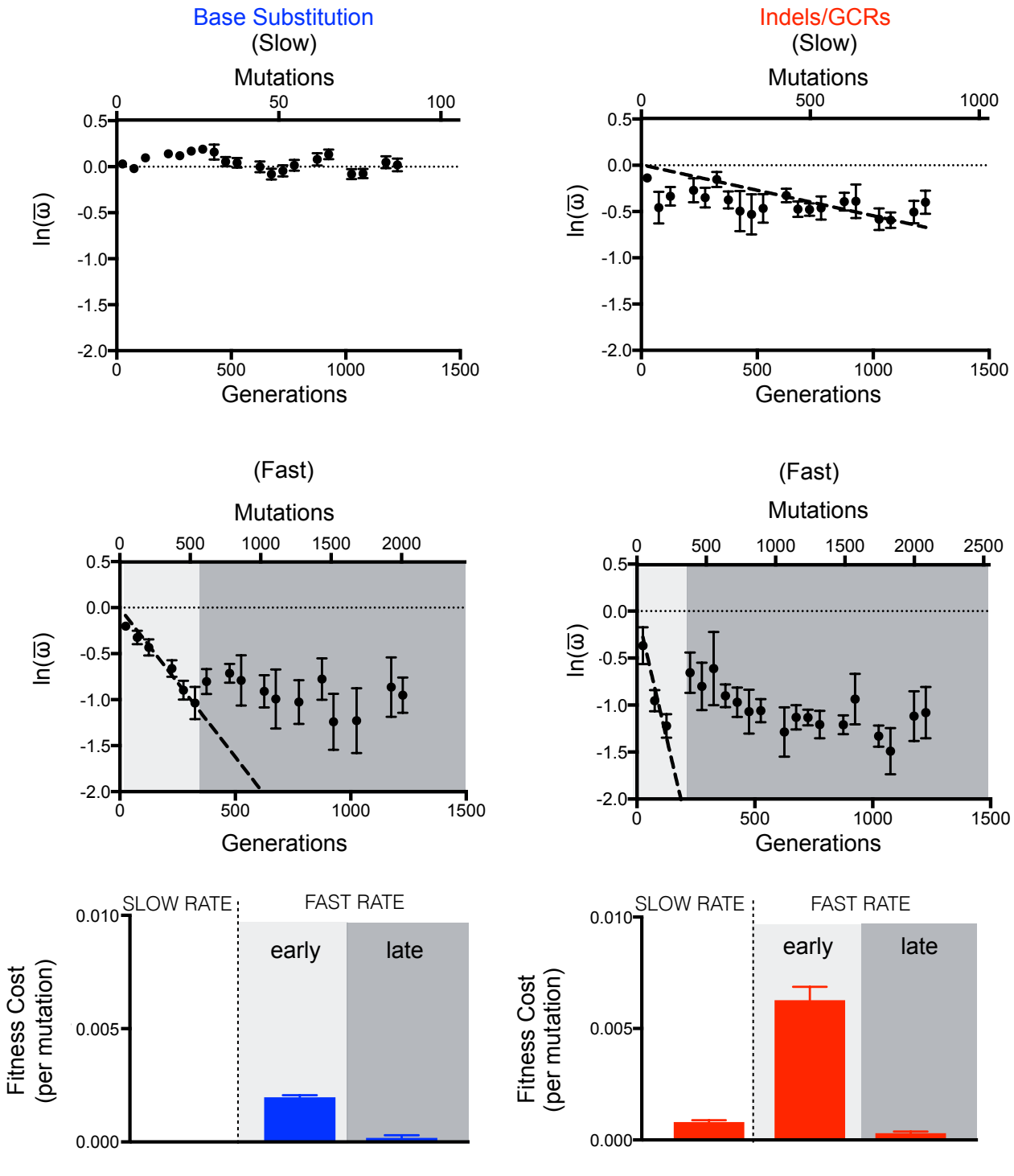




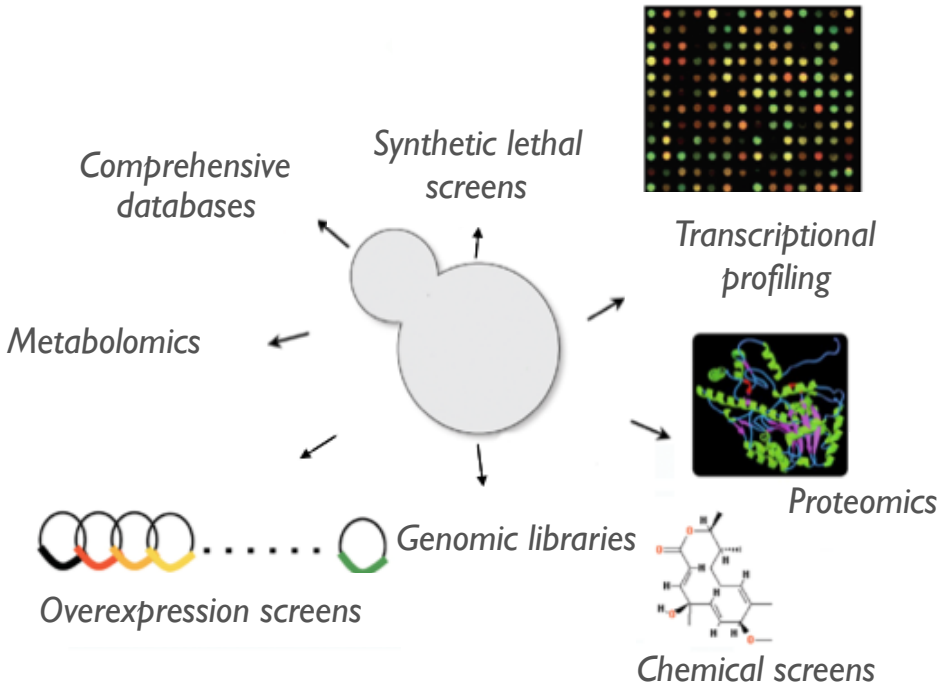

Base Substitution
(Slow)
Mutations
0
50
100
0.5
0.0
-0.5
-1.0
-1.5
-2.0
ln(ω̄)
0
500
1000
1500
Generations


Base Substitution
(Slow)
Mutations
0
50
100
0.5
0.0
-0.5
-1.0
-1.5
-2.0
ln(ω̄)
0
500
1000
1500
Generations
Indels/GCRs
(Slow)
Mutations
0
500
1000
0.5
0.0
-0.5
-1.0
-1.5
-2.0
ln(ω̄)
0
500
1000
1500
Generations


Base Substitution
(Slow)
Mutations
0
50
100
0.5
0.0
-0.5
-1.0
-1.5
-2.0
ln(ω̄)
0
500
1000
1500
Generations
Indels/GCRs
(Slow)
Mutations
0
500
1000
0.5
0.0
-0.5
-1.0
-1.5
-2.0
ln(ω̄)
0
500
1000
1500
Generations
(Fast)
Mutations
0
500
1000
1500
2000
0.5
0.0
-0.5
-1.0
-1.5
-2.0
ln(ω̄)
0
500
1000
1500
Generations
(Fast)
Mutations
0
500
1000
1500
2000
2500
0.5
0.0
-0.5
-1.0
-1.5
-2.0
ln(ω̄)
0
500
1000
1500
Generations


Base Substitution
(Slow)
Mutations
0
50
100
0.5
0.0
-0.5
-1.0
-1.5
-2.0
ln(ω̄)
0
500
1000
1500
Generations
Indels/GCRs
(Slow)
Mutations
0
500
1000
0.5
0.0
-0.5
-1.0
-1.5
-2.0
ln(ω̄)
0
500
1000
1500
Generations
(Fast)
Mutations
0
500
1000
1500
2000
0.5
0.0
-0.5
-1.0
-1.5
-2.0
ln(ω̄)
0
500
1000
1500
Generations
(Fast)
Mutations
0
500
1000
1500
2000
2500
0.5
0.0
-0.5
-1.0
-1.5
-2.0
ln(ω̄)
0
500
1000
1500
Generations
SLOW RATE
FAST RATE
early
late
0.010
0.005
0.000
Fitness Cost
(per mutation)
SLOW RATE
FAST RATE
early
late
0.010
0.005
0.000
Fitness Cost
(per mutation)

How do these cells 'buffer' the consequences of their mutation burden?



-Genomic analyses to understand how these cells withstand high mutation burden — a new 'mutation stress response'

-Chemical screens to identify unique vulnerabilities

-Can these robustness mechanisms be perturbed or even exploited therapeutically in highly mutating cancers and pathogens?