

## Supplementary Material

Paper: Modelling the onset of senescence at the G1/S cell cycle checkpoint

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Stable states for the wild type situation and a range of perturbations corresponding to Loss-of-Function (LoF) and Gain-of-Function (GoF) *in silico* experiments (see also Table 3). Results were obtained using GINsim. For a LoF, the component value is constrained to value 0, whereas for a GoF the value is constrained to value 1 (for a Boolean case), or within a range of positive values (indicated between square brackets). States are displayed in the same way as in Figure 2. Each of the 9 combinations of SSB and DSB values (2 right-most columns) leads to a unique stable state denoting a cell fate defined by the values of the outputs (4 left-most columns). Below each table, a short interpretation indicates the main phenotypic changes compared to the wild type situation.

Wild type case																				
apoptosis	cyclearrest	senescence	proliferation	CHEK1	CHEK2	Mdm2	p14ARF	p53	p21	RB1	p16INK4a	p38MAPK	CDK46CycD	Cdc25A	CDK2CycE	E2F	ATM	ATR	DSB	SSB
			1				1						1	2	1	1				
	1					1		1	1	1	1	1		1				1		1
	1					1		1	1	1	1	1		1			1		1	
	1					1		1	1	1	1	1		1			1	1	1	1
	1			1		1		1	1	1	1	1		1				2		2
	1			1		1		1	1	1	1	1		1			1	2	1	2
	1	1		1	1	1		1	1	1	1	2					2		2	
	1	1		1	1	1		1	1	1	1	2					2	1	2	1
1	1			1	1		1	2	1	1	2	3					2	2	2	2

CHEK2 LoF																				
apoptosis	cyclearrest	senescence	proliferation	CHEK1	CHEK2	Mdm2	p14ARF	p53	p21	RB1	p16INK4a	p38MAPK	CDK46CycD	Cdc25A	CDK2CycE	E2F	ATM	ATR	DSB	SSB
			1				1						1	2	1	1				
	1					1		1	1	1	1	1		1				1		1
	1					1		1	1	1	1	1		1			1		1	
	1					1		1	1	1	1	1		1			1	1	1	1
	1			1		1		1	1	1	1	1		1				2		2
	1			1		1		1	1	1	1	1		1			1	2	1	2
	1			1		1		1	1	1	1	2		1			2		2	
	1			1		1		1	1	1	1	2		1			2	1	2	1
1	1			1			1	2	1	1	2	3		1			2	2	2	2

Without DNA damage: proliferation  
With DNA damage: loss of senescence

### CHEK2 GoF

	apoptosis	cyclearrest	senescence	proliferation	CHEK1	CHEK2	Mdm2	p14ARF	p53	p21	RB1	p16INK4a	p38MAPK	CDK46CycD	Cdc25A	CDK2CycE	E2F	ATM	ATR	DSB	SSB
	1				1	1		1	1	1	1			1							
	1				1	1		1	1	1	1	1	1		1				1		1
	1				1	1		1	1	1	1	1	1		1			1		1	1
	1				1	1		1	1	1	1	1	1		1			1	1	1	1
	1	1			1	1		1	1	1	1	1	1					2		2	2
	1	1			1	1		1	1	1	1	1	1					1	2	1	2
	1	1			1	1		1	1	1	1	1	2					2		2	
	1	1			1	1		1	1	1	1	1	2					2	1	2	1
1	1				1	1		1	2	1	1	2	3					2	2	2	2

Without DNA damage: loss of proliferation

With DNA damage: senescence enhanced

### CHEK1 LoF

	apoptosis	cyclearrest	senescence	proliferation	CHEK1	CHEK2	Mdm2	p14ARF	p53	p21	RB1	p16INK4a	p38MAPK	CDK46CycD	Cdc25A	CDK2CycE	E2F	ATM	ATR	DSB	SSB
				1				1						1	2	1	1				
	1						1	1	1	1	1	1	1		1				1		1
	1						1	1	1	1	1	1	1		1				2		2
	1						1	1	1	1	1	1	1		1			1		1	1
	1						1	1	1	1	1	1	1		1			1	1	1	1
	1						1	1	1	1	1	1	1		1			1	2	1	2
	1				1	1		1	1	1	1	1	2		1			2		2	
	1				1	1		1	1	1	1	1	2		1			2	1	2	1
1	1				1		1	2	1	1	1	2	3		1			2	2	2	2

Without DNA damage: proliferation

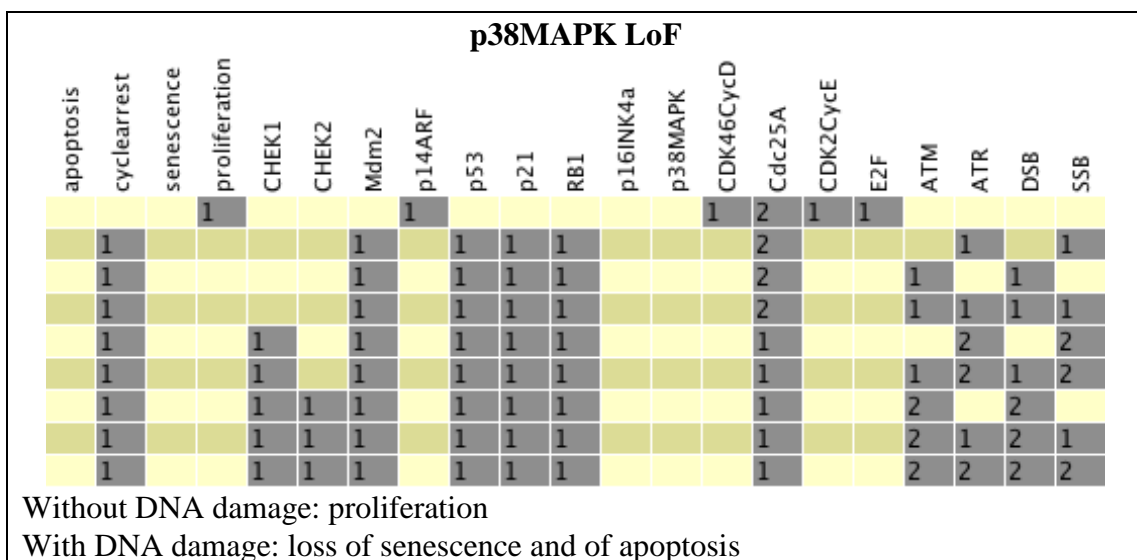
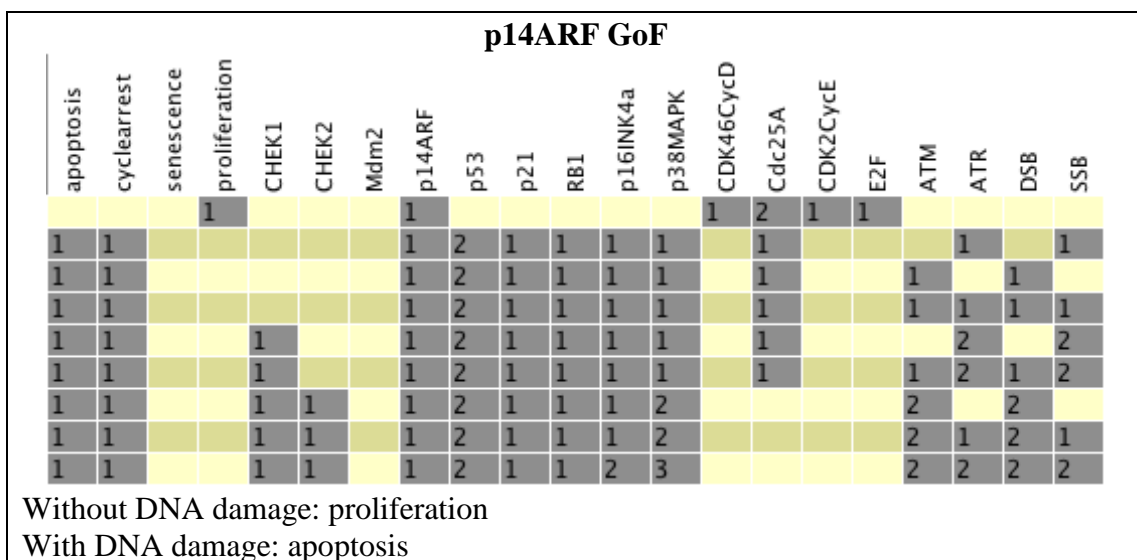
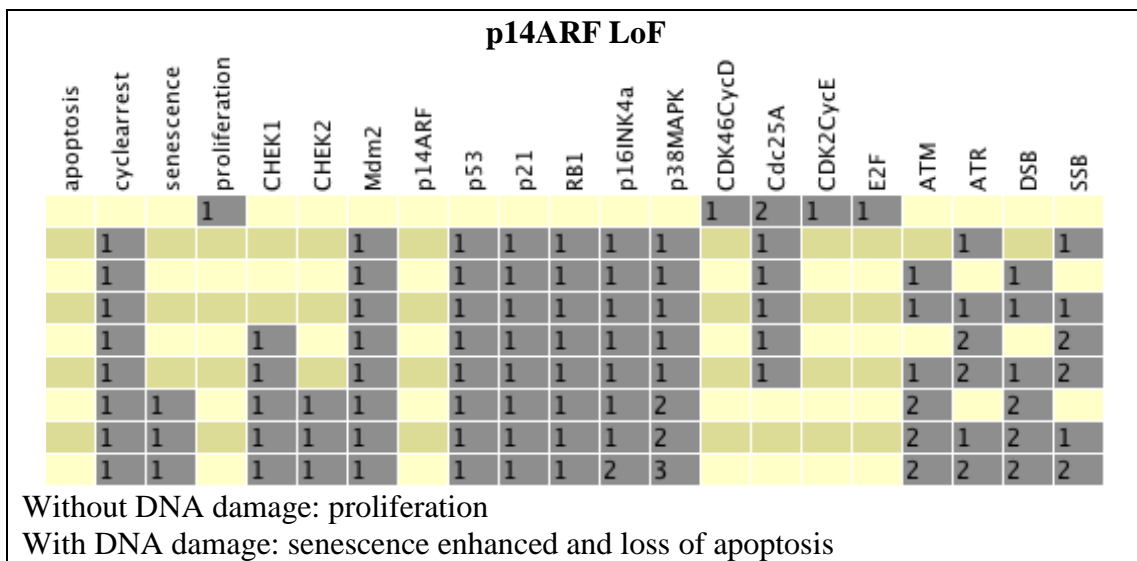
With DNA damage: loss of senescence

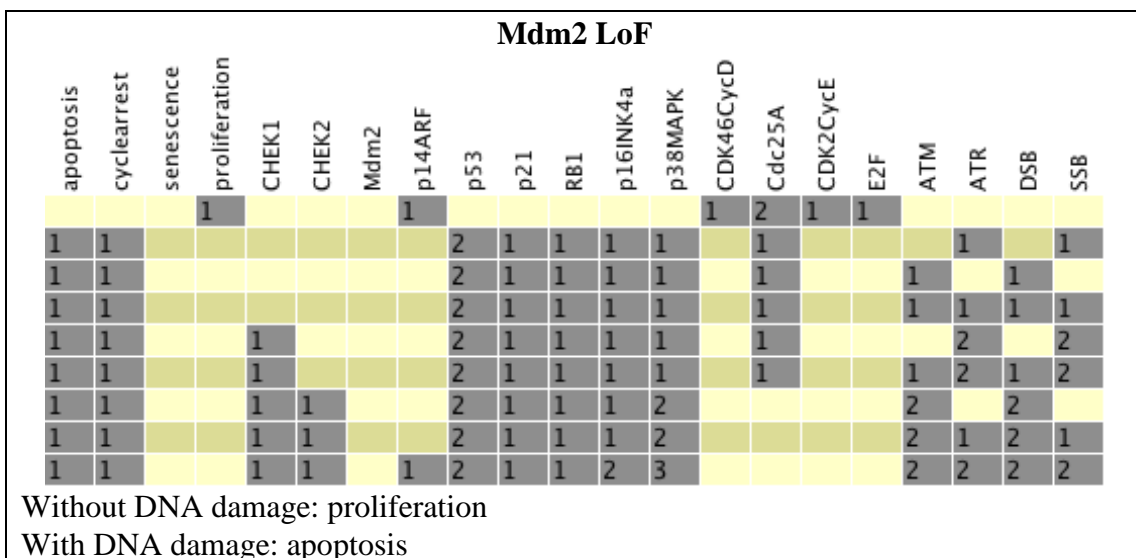
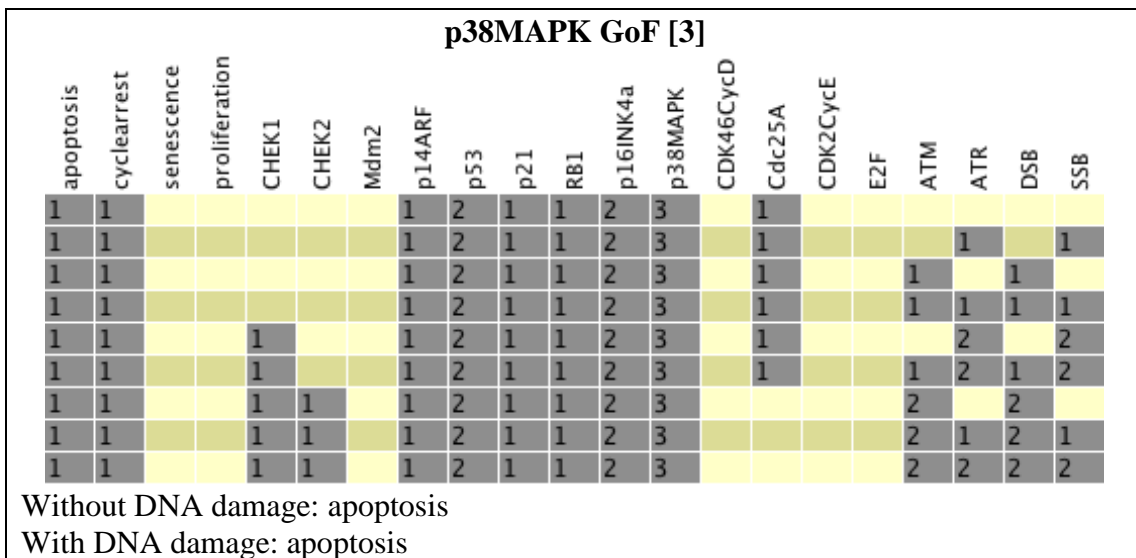
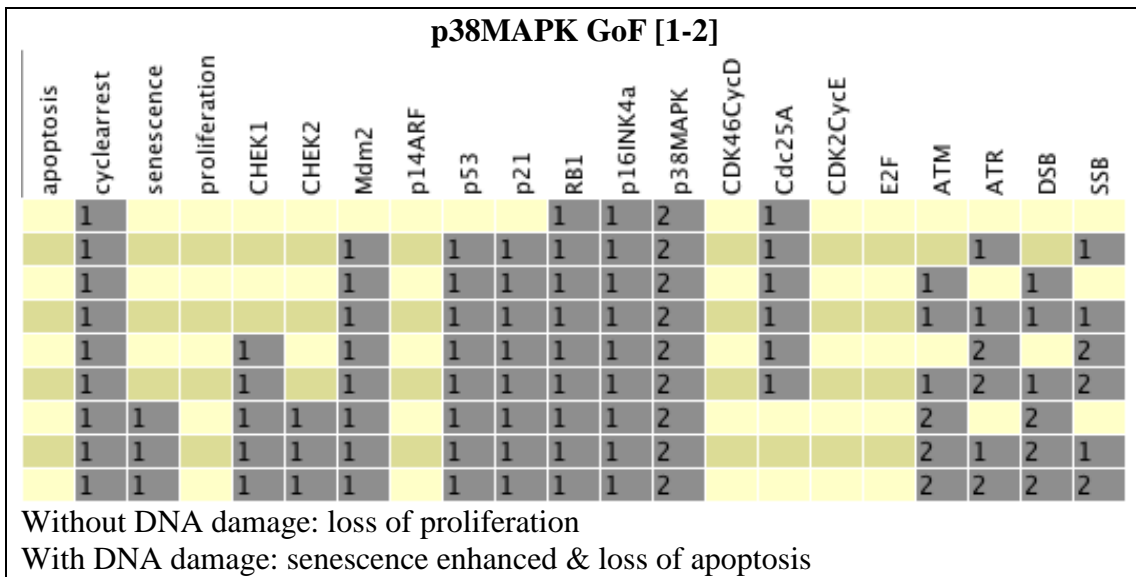
### CHEK1 GoF

	apoptosis	cyclearrest	senescence	proliferation	CHEK1	CHEK2	Mdm2	p14ARF	p53	p21	RB1	p16INK4a	p38MAPK	CDK46CycD	Cdc25A	CDK2CycE	E2F	ATM	ATR	DSB	SSB
					1		1		1	1	1				1						
	1				1		1		1	1	1	1	1		1				1		1
	1				1		1		1	1	1	1	1		1				2		2
	1				1		1		1	1	1	1	1		1			1		1	1
	1				1		1		1	1	1	1	1		1			1	1	1	1
	1				1		1		1	1	1	1	1		1			1	2	1	2
	1	1			1	1		1	1	1	1	1	2					2		2	
	1	1			1	1		1	1	1	1	1	2					2	1	2	1
1	1				1	1		1	2	1	1	2	3					2	2	2	2

Without DNA damage: loss of proliferation

With DNA damage: similar to the wild type





### Mdm2 GoF

	apoptosis	cyclearrest	senescence	proliferation	CHEK1	CHEK2	Mdm2	p14ARF	p53	p21	RBI	p16INK4a	p38MAPK	CDK46CycD	Cdc25A	CDK2CycE	E2F	ATM	ATR	DSB	SSB	
				1			1	1						1	2	1	1					
	1						1	1	1	1	1	1	1		1				1			1
	1						1	1	1	1	1	1	1		1			1		1		
	1				1		1	1	1	1	1	1	1		1					2		2
	1				1		1	1	1	1	1	1	1		1			1	2	1	2	2
	1	1			1	1	1	1	1	1	1	1	2					2		2		
	1	1			1	1	1	1	1	1	1	1	2					2	1	2	2	1
	1	1			1	1	1	1	1	1	1	2	3					2	2	2	2	2

Without DNA damage: proliferation

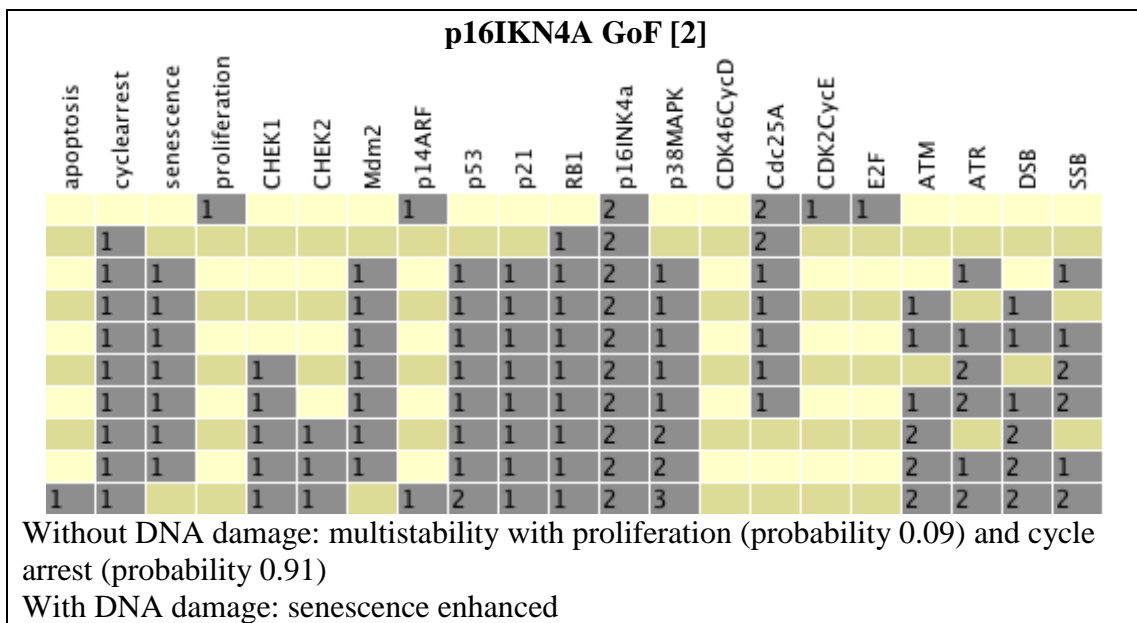
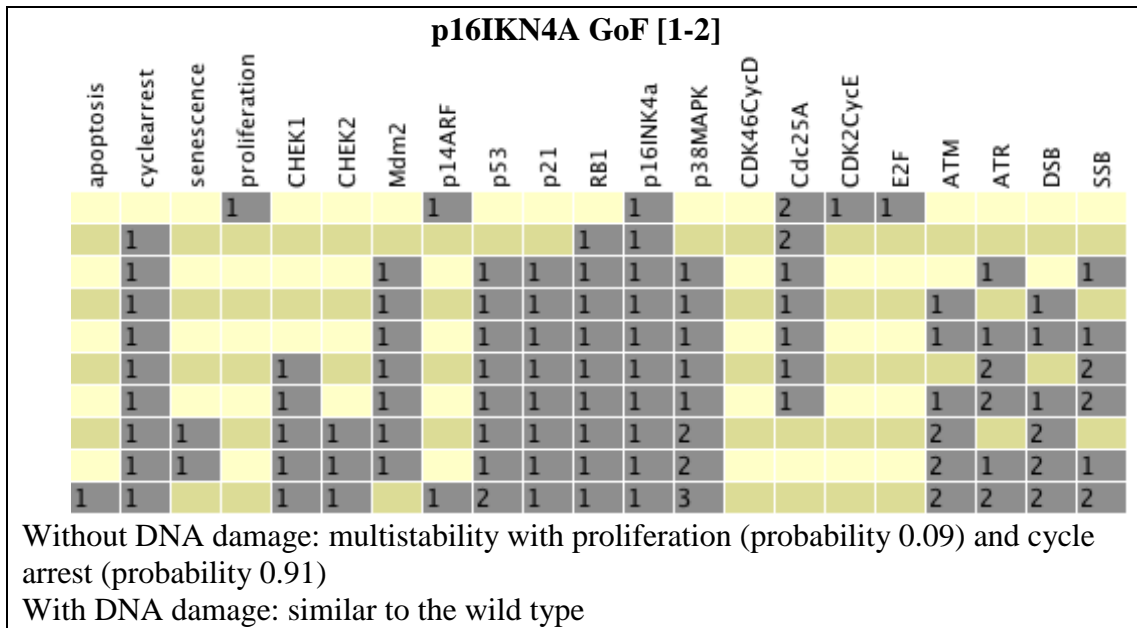
With DNA damage: senescence enhanced & loss of apoptosis

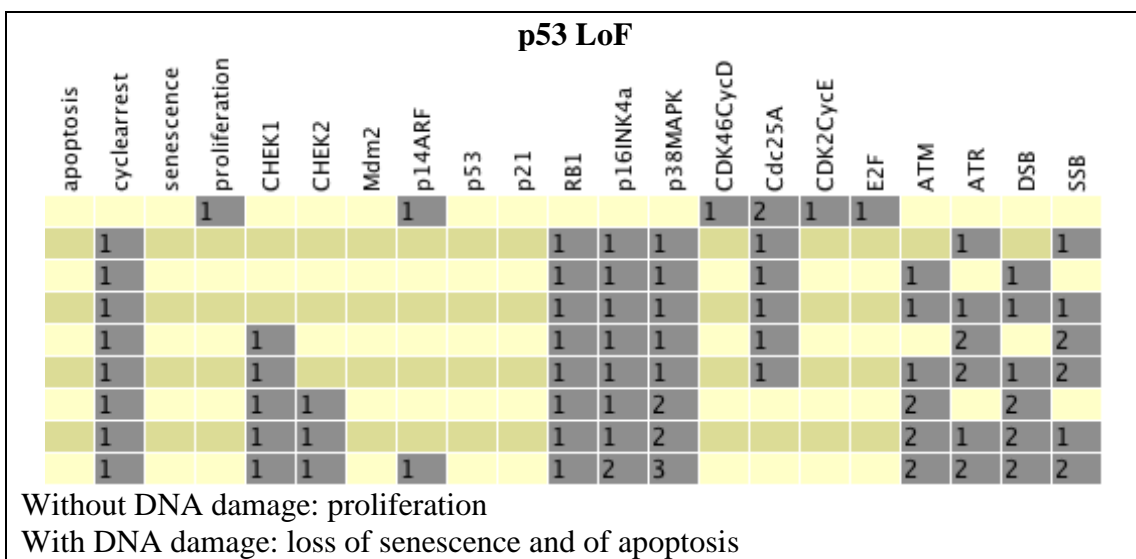
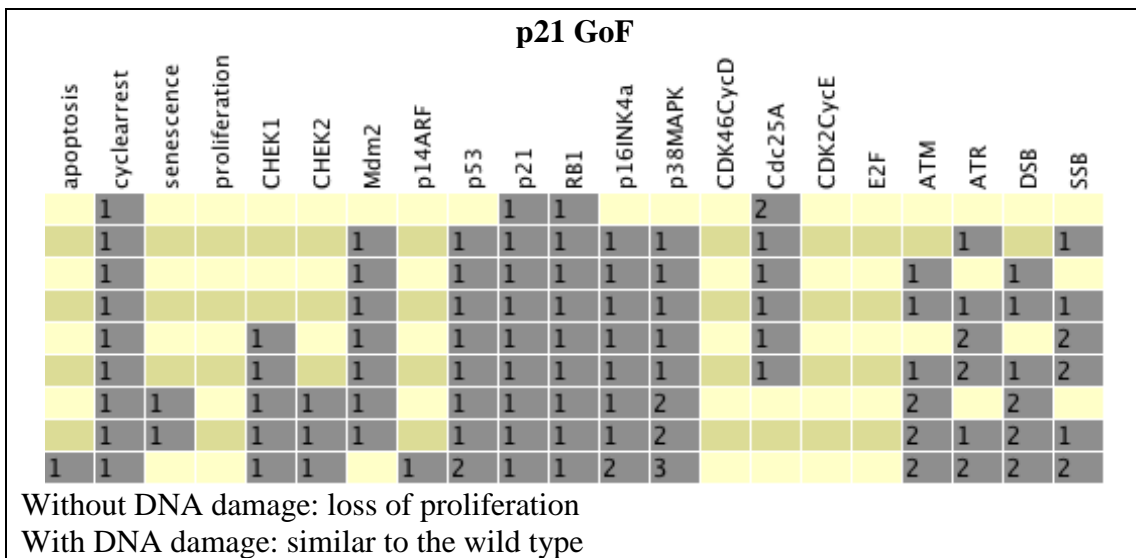
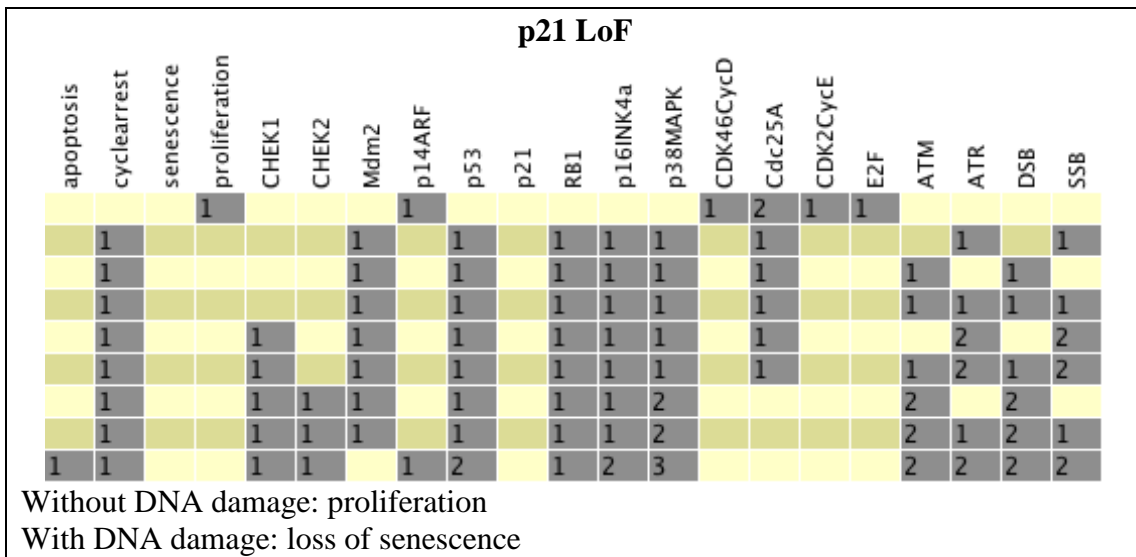
### p16INK4A LoF

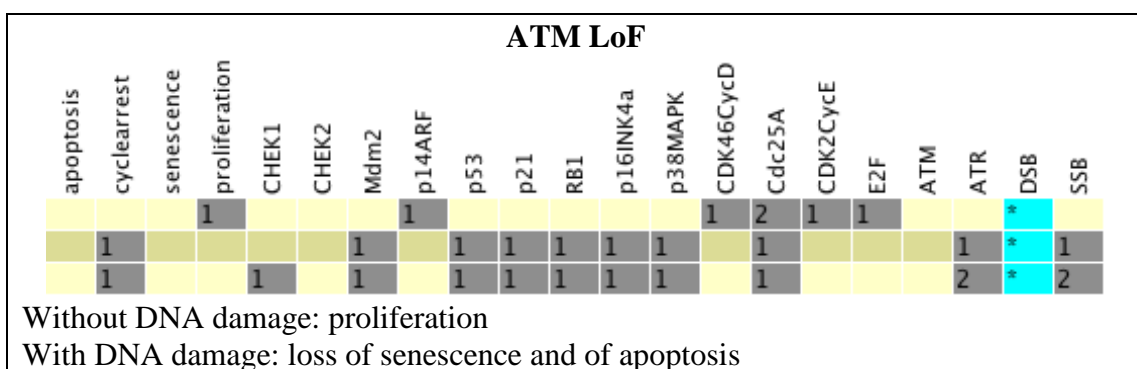
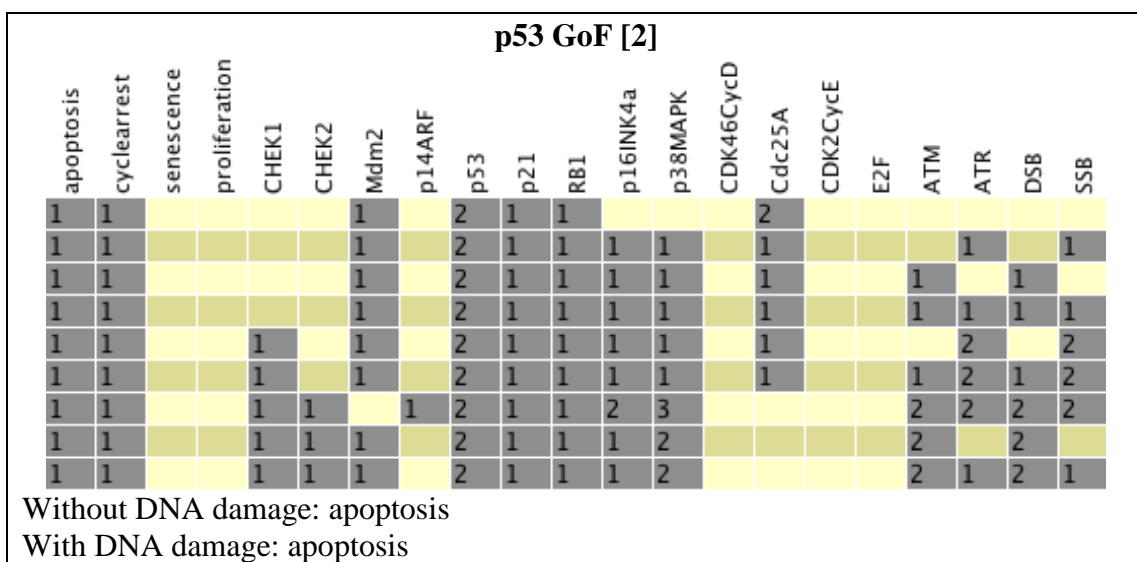
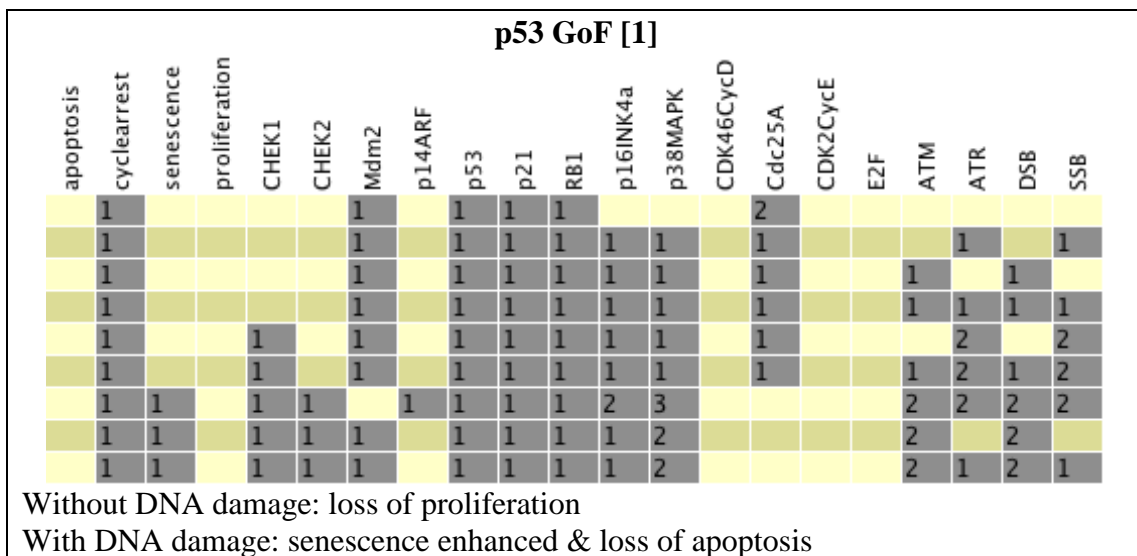
	apoptosis	cyclearrest	senescence	proliferation	CHEK1	CHEK2	Mdm2	p14ARF	p53	p21	RBI	p16INK4a	p38MAPK	CDK46CycD	Cdc25A	CDK2CycE	E2F	ATM	ATR	DSB	SSB	
				1				1						1	2	1	1					
	1						1	1	1	1	1		1		1				1			1
	1						1	1	1	1	1		1		1			1		1		
	1				1		1	1	1	1	1		1		1					2		2
	1				1		1	1	1	1	1		1		1			1	2	1	2	2
	1				1	1	1	1	1	1	1		2					2		2		
	1				1	1	1	1	1	1	1		2					2	1	2	2	1
	1	1			1	1		1	2	1	1		3					2	2	2	2	2

Without DNA damage: proliferation

With DNA damage: loss of senescence









### ATM GoF [1]

	apoptosis	cyclearrest	senescence	proliferation	CHEK1	CHEK2	Mdm2	p14ARF	p53	p21	RB1	p16INK4a	p38MAPK	CDK46CycD	Cdc25A	CDK2CycE	E2F	ATM	ATR	DSB	SSB	
Without DNA damage:	1																					
With DNA damage:	1																	1	1	*		
	1			1			1		1	1	1	1	1		1			1	2	*	2	

Without DNA damage: loss of proliferation

With DNA damage: loss of senescence and of apoptosis

### ATM GoF [2]

	apoptosis	cyclearrest	senescence	proliferation	CHEK1	CHEK2	Mdm2	p14ARF	p53	p21	RB1	p16INK4a	p38MAPK	CDK46CycD	Cdc25A	CDK2CycE	E2F	ATM	ATR	DSB	SSB	
Without DNA damage:		1	1		1	1	1		1	1	1	1	2					2				
With DNA damage:	1	1			1	1		1	2	1	1	2	3					2	2	*	*	1
				1	1	1		1	1	1	1	1	2					2	2	*	*	2

Without DNA damage: senescence

With DNA damage: senescence enhanced

### ATR LoF

	apoptosis	cyclearrest	senescence	proliferation	CHEK1	CHEK2	Mdm2	p14ARF	p53	p21	RB1	p16INK4a	p38MAPK	CDK46CycD	Cdc25A	CDK2CycE	E2F	ATM	ATR	DSB	SSB	
Without DNA damage:				1				1						1	2	1	1					*
With DNA damage:	1						1		1	1	1	1	1		1			1		1	*	*
	1	1			1	1	1		1	1	1	2						2		2	*	*

Without DNA damage: proliferation

With DNA damage: senescence enhanced & loss of apoptosis

### ATR GoF [1]

	apoptosis	cyclearrest	senescence	proliferation	CHEK1	CHEK2	Mdm2	p14ARF	p53	p21	RB1	p16INK4a	p38MAPK	CDK46CycD	Cdc25A	CDK2CycE	E2F	ATM	ATR	DSB	SSB	
Without DNA damage:		1					1		1	1	1	1	1		1					1		*
With DNA damage:	1	1					1		1	1	1	1	1		1			1	1	1	*	*
	1	1			1	1	1		1	1	1	2						2	1	2	*	*

Without DNA damage: loss of proliferation

With DNA damage: senescence enhanced & loss of apoptosis

**ATR GoF [2]**

	apoptosis	cyclearrest	senescence	proliferation	CHEK1	CHEK2	Mdm2	p14ARF	p53	p21	RB1	p16INK4a	p38MAPK	CDK46CycD	Cdc25A	CDK2CycE	E2F	ATM	ATR	DSB	SSB	
	1	1			1		1	1	1	1	1	1	1		1				2			*
	1	1			1		1	1	1	1	1	1	1		1			1	2	1		*
	1	1			1	1		1	2	1	1	2	3					2	2	2		*

Without DNA damage: loss of proliferation  
 With DNA damage: loss of senescence & apoptosis enhanced

**RB1 LoF**

	apoptosis	cyclearrest	senescence	proliferation	CHEK1	CHEK2	Mdm2	p14ARF	p53	p21	RB1	p16INK4a	p38MAPK	CDK46CycD	Cdc25A	CDK2CycE	E2F	ATM	ATR	DSB	SSB	
	1	1		1				1	2	1		1	1	1	2	1	1			1		1
	1	1						1	2	1		1	1	1	1	1	1	1		1	1	1
	1	1						1	2	1		1	1	1	1	1	1	1		1	1	1
	1	1			1			1	2	1		1	1	1	1	1	1	1		2	1	2
	1	1			1			1	2	1		1	1	1	1	1	1	1		2	1	2
	1	1			1	1		1	2	1		1	2		1	1	1	2		2	1	2
	1	1			1	1		1	2	1		1	2		1	1	1	2		2	1	2
	1	1			1	1		1	2	1		2	3				1	2	2	2	2	2

Without DNA damage: proliferation  
 With DNA damage: apoptosis

**RB1 GoF**

	apoptosis	cyclearrest	senescence	proliferation	CHEK1	CHEK2	Mdm2	p14ARF	p53	p21	RB1	p16INK4a	p38MAPK	CDK46CycD	Cdc25A	CDK2CycE	E2F	ATM	ATR	DSB	SSB	
		1									1			1	2							
		1					1		1	1	1	1	1	1	1				1			1
		1					1		1	1	1	1	1	1	1			1		1		
		1					1		1	1	1	1	1	1	1			1	1	1	1	1
		1			1		1		1	1	1	1	1	1	1			1	2		2	2
		1			1		1		1	1	1	1	1	1	1			1	2	1	1	2
		1	1		1	1	1		1	1	1	1	2					2		2		
		1	1		1	1	1		1	1	1	1	2					2	1	2		1
	1	1			1	1		1	2	1	1	2	3					2	2	2		2

Without DNA damage: loss of proliferation  
 With DNA damage: similar to the wild type

### CDC25A LoF

	apoptosis	cyclearrest	senescence	proliferation	CHEK1	CHEK2	Mdm2	p14ARF	p53	p21	RB1	p16INK4a	p38MAPK	CDK46CycD	Cdc25A	CDK2CycE	E2F	ATM	ATR	DSB	SSB	
1	1				1	1		1	2	1	1	2	3				2	2	2	2	2	
2	1	1					1	1	1	1	1	1	1									1
3	1	1					1	1	1	1	1	1	1					1		1	1	1
4	1	1					1	1	1	1	1	1	1					1	1	1	1	1
5	1	1			1		1	1	1	1	1	1	1						2		2	2
6	1	1			1		1	1	1	1	1	1	1					1	2	1	2	2
7	1	1			1	1	1	1	1	1	1	2						2		2		
8	1	1			1	1	1	1	1	1	1	2						2	1	2	2	1

Without DNA damage: loss of proliferation  
 With DNA damage: senescence enhanced

### CDC25A GoF [1-2]

	apoptosis	cyclearrest	senescence	proliferation	CHEK1	CHEK2	Mdm2	p14ARF	p53	p21	RB1	p16INK4a	p38MAPK	CDK46CycD	Cdc25A	CDK2CycE	E2F	ATM	ATR	DSB	SSB	
1	1	1			1	1		1	2	1	1	2	3		1			2	2	2	2	2
2		1					1	1	1	1	1	1	1	1	2	1				1		1
3		1					1	1	1	1	1	1	1	1	1	1			1	1	1	1
4		1					1	1	1	1	1	1	1	1	1	1			1	1	1	1
5		1			1		1	1	1	1	1	1	1						2		2	2
6		1			1		1	1	1	1	1	1	1					1	2	1	2	2
7		1			1	1	1	1	1	1	1	2						2		2		
8		1			1	1	1	1	1	1	1	2						2	1	2	2	1

Without DNA damage: proliferation  
 With DNA damage: loss of senescence

### E2F LoF

	apoptosis	cyclearrest	senescence	proliferation	CHEK1	CHEK2	Mdm2	p14ARF	p53	p21	RB1	p16INK4a	p38MAPK	CDK46CycD	Cdc25A	CDK2CycE	E2F	ATM	ATR	DSB	SSB	
1	1	1			1	1		1	2	1	1	2	3					2	2	2	2	2
2		1					1	1	1	1	1	1	1	1	2	1				1		1
3		1					1	1	1	1	1	1	1	1	1	1			1		1	1
4		1					1	1	1	1	1	1	1	1	1	1			1	1	1	1
5		1			1		1	1	1	1	1	1	1						2		2	2
6		1			1		1	1	1	1	1	1	1					1	2	1	2	2
7		1	1		1	1	1	1	1	1	1	2						2		2		
8		1	1		1	1	1	1	1	1	1	2						2	1	2	2	1

Without DNA damage: loss of proliferation  
 With DNA damage: similar to the wild type

### E2F GoF

	apoptosis	cyclearrest	senescence	proliferation	CHEK1	CHEK2	Mdm2	p14ARF	p53	p21	RB1	p16INK4a	p38MAPK	CDK46CycD	Cdc25A	CDK2CycE	E2F	ATM	ATR	DSB	SSB	
				1				1						1	2	1	1					
1	1							1	2	1	1	1	1		1		1		1			1
1	1							1	2	1	1	1	1		1		1	1		1		
1	1							1	2	1	1	1	1		1		1	1	1	1	1	1
1	1				1			1	2	1	1	1	1		1		1		2			2
1	1				1			1	2	1	1	1	1		1		1	1	2	1	2	2
1	1				1	1		1	2	1	1	1	2				1	2		2		
1	1				1	1		1	2	1	1	1	2				1	2	1	2	2	1
1	1				1	1		1	2	1	1	2	3				1	2	2	2	2	2

Without DNA damage: proliferation

With DNA damage: apoptosis

### p53 and Mdm2 LoF (double mutant)

	apoptosis	cyclearrest	senescence	proliferation	CHEK1	CHEK2	Mdm2	p14ARF	p53	p21	RB1	p16INK4a	p38MAPK	CDK46CycD	Cdc25A	CDK2CycE	E2F	ATM	ATR	DSB	SSB	
				1				1						1	2	1	1					
	1										1	1	1		1				1			1
	1										1	1	1		1				1		1	
	1				1						1	1	1		1				2			2
	1				1						1	1	1		1			1	2	1	2	2
	1				1	1					1	1	2					2		2		
	1				1	1					1	1	2					2	1	2	2	1
	1				1	1		1			1	2	3					2	2	2	2	2

Without DNA damage: proliferation

With DNA damage: loss of senescence and of apoptosis