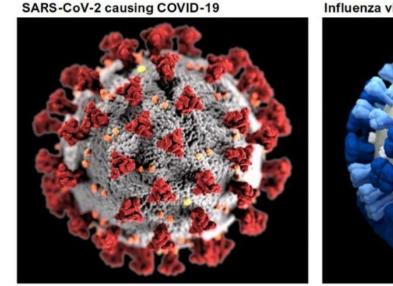


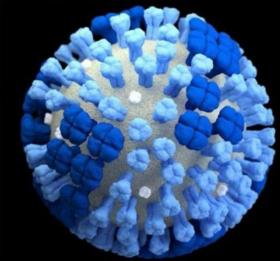
ADAM MICKIEWICZ UNIVERSITY IN POZNAŃ

**Faculty of Biology** 

#### Time-dependent IFN-induced Chromatin Interactions & Gene Transcription Shape the Antiviral Response



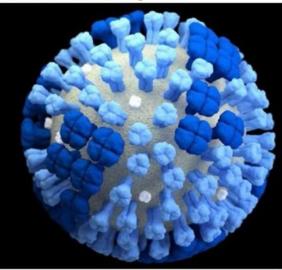
Influenza virus causing the flu



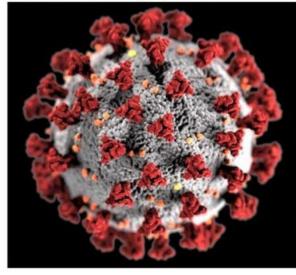
#### Hans Bluyssen, 21.01.2022

www.amu.edu.pl

#### Influenza virus causing the flu



#### SARS-CoV-2 causing COVID-19

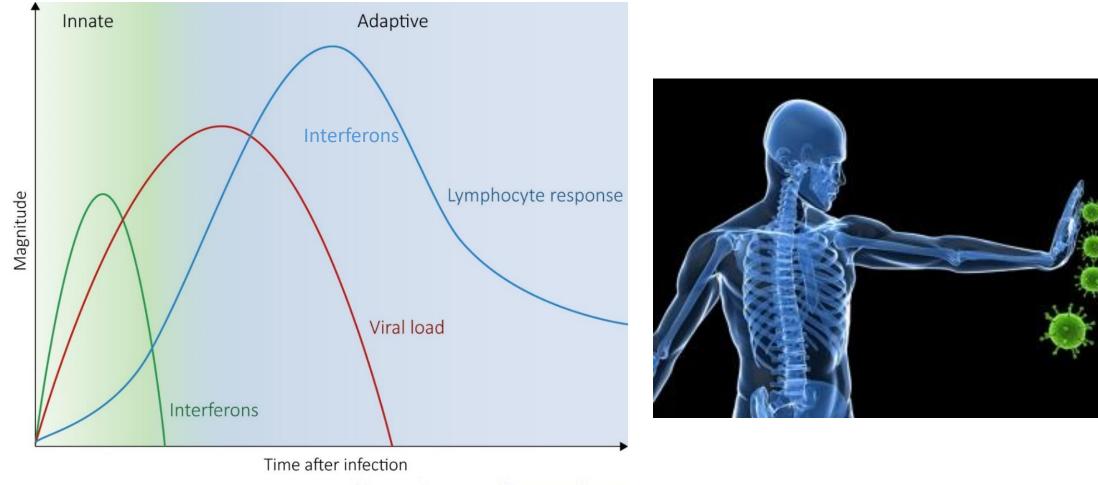


## **Viral Infection**



# What is happening?

### Anti-viral Response & IFNs



Nature Reviews | Immunology



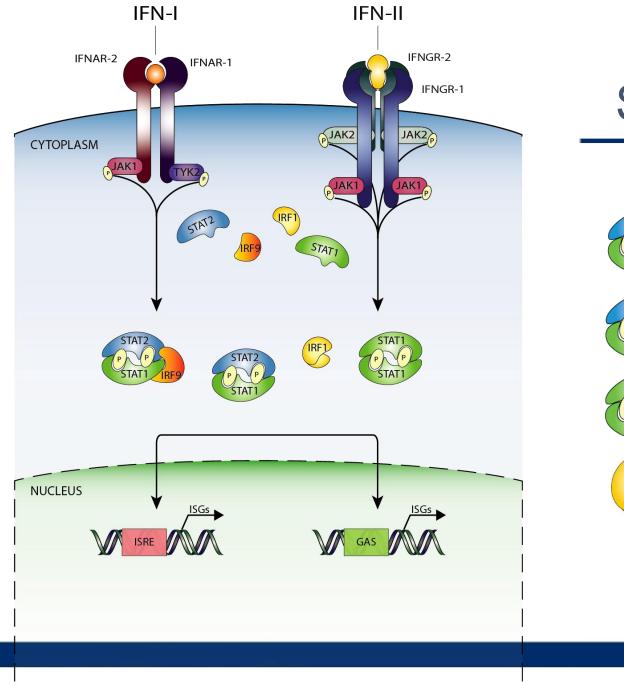
**Interferons (IFNs)** are released by <u>host cells</u> in response to the presence of many <u>viruses</u> causing nearby <u>cells</u> to heighten their anti-viral defenses.

**IFN**s belong to the large class of <u>proteins</u> known as <u>cytokines</u>, molecules used for communication between cells to trigger the protective defenses of the <u>immune system</u> that help eradicate pathogens.

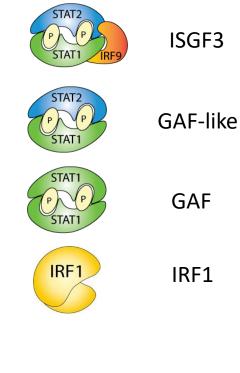
**IFN**s are named for their ability to "interfere" with <u>viral replication<sup>[3]</sup></u> by protecting cells from <u>virus</u> <u>infections</u>.

**IFN**s also have various other functions: they activate <u>immune cells</u>, such as <u>natural killer cells</u> and <u>macrophages</u>; they increase host defenses by up-regulating <u>antigen presentation</u> by virtue of increasing the expression of <u>major histocompatibility complex</u> (MHC) <u>antigens</u>.

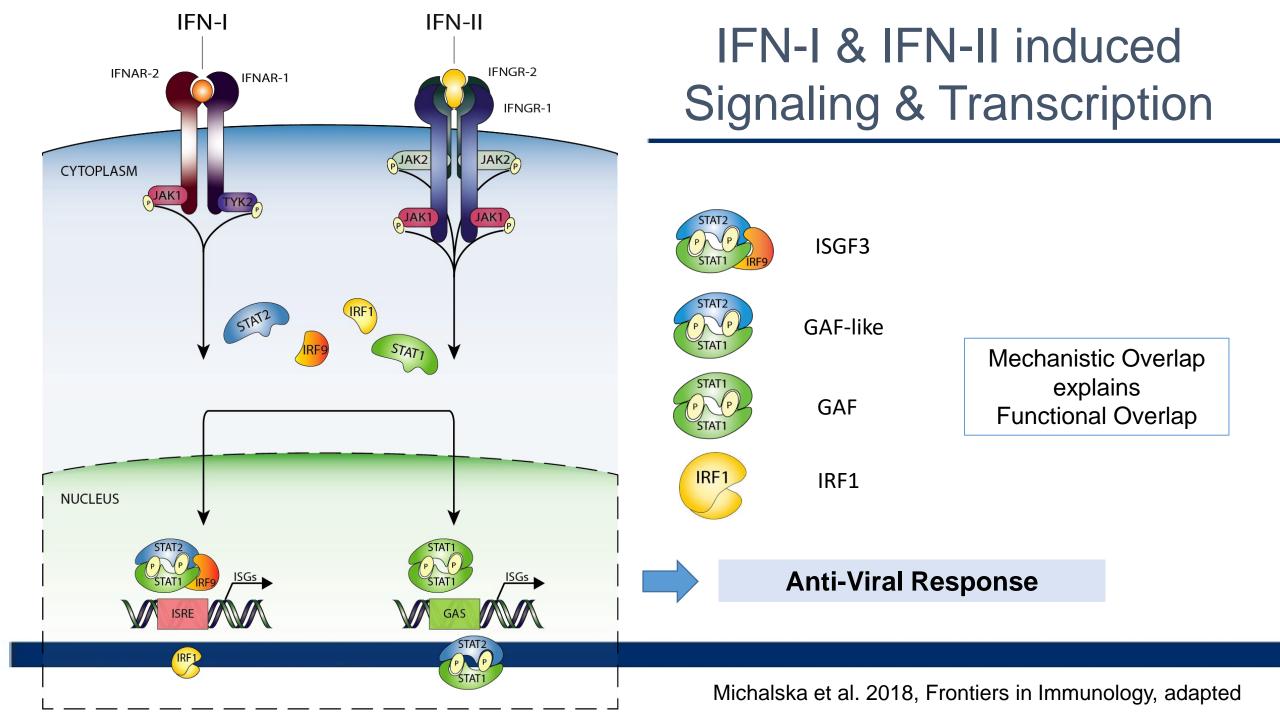
Certain symptoms of infections, such as <u>fever</u>, <u>muscle pain</u> and "flu-like symptoms", are also caused by the production of **IFN**s and other <u>cytokines</u>.

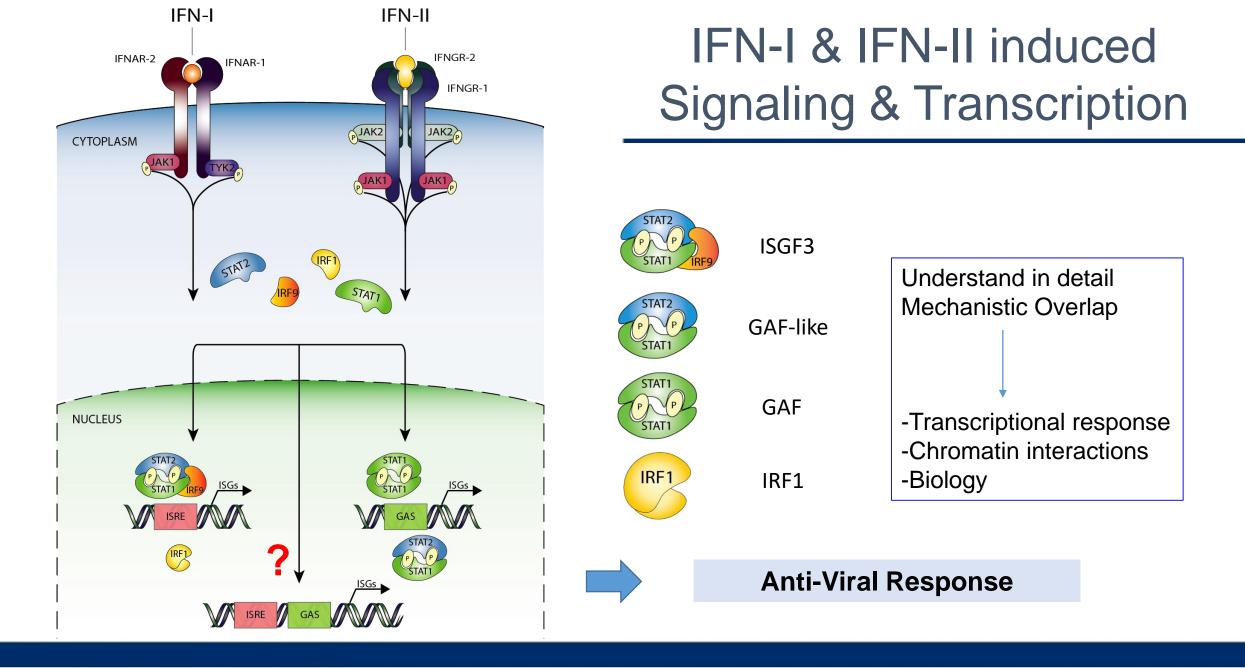


# IFN-I & IFN-II induced Signaling & Transcription



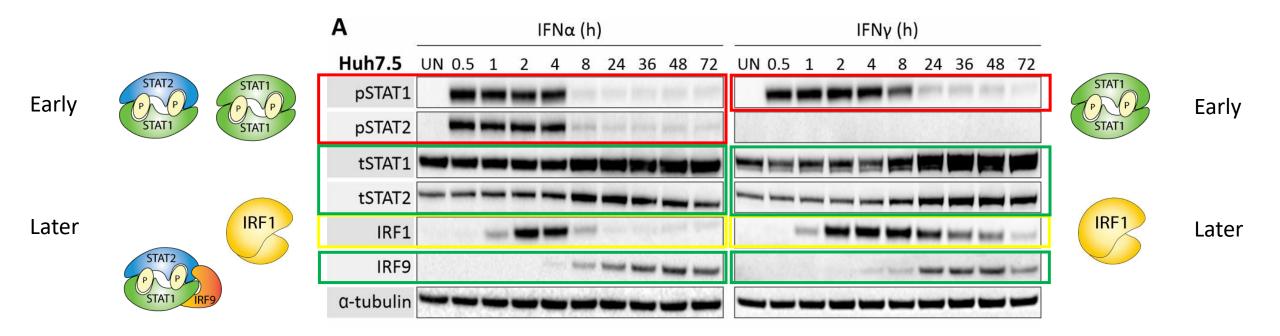
#### Michalska et al. 2018, Frontiers in Immunology, adapted





Michalska et al. 2018, Frontiers in Immunology, adapted

## IFN-signaling <u>In Time</u>: pSTAT1, pSTAT2, IRF9 & IRF1

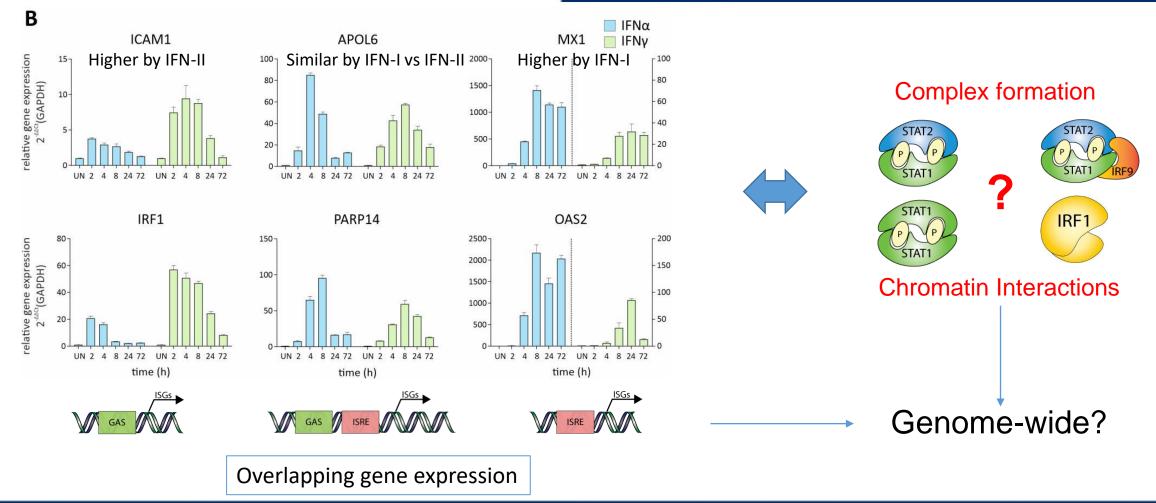


Common signaling mechanisms

Yamauchi et al., Scientific Rep 2016

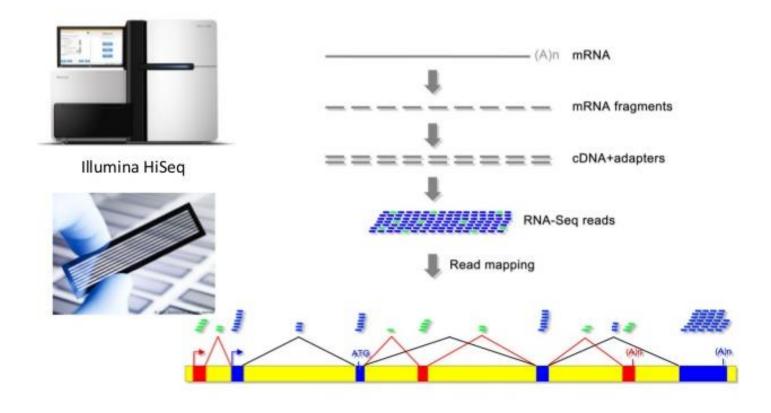
# IFN-I & IFN-II induced Transcriptional Response in Time

Representative genes



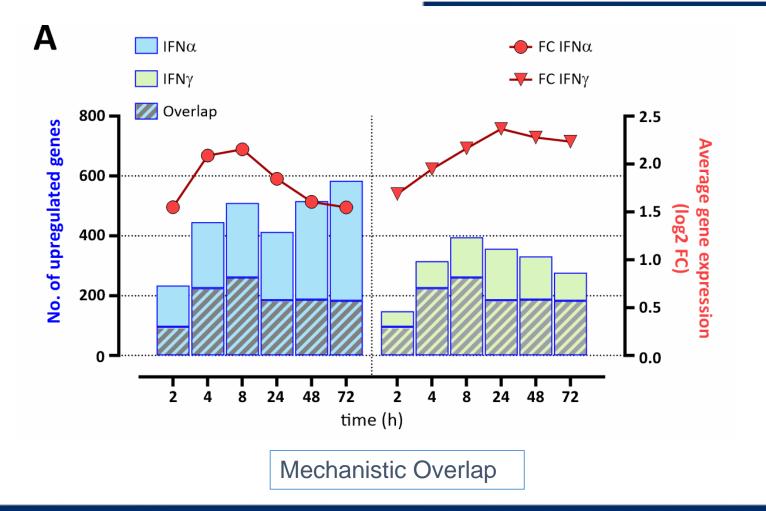
How to analyze the transcriptome?

### **RNA-seq Work Flow**

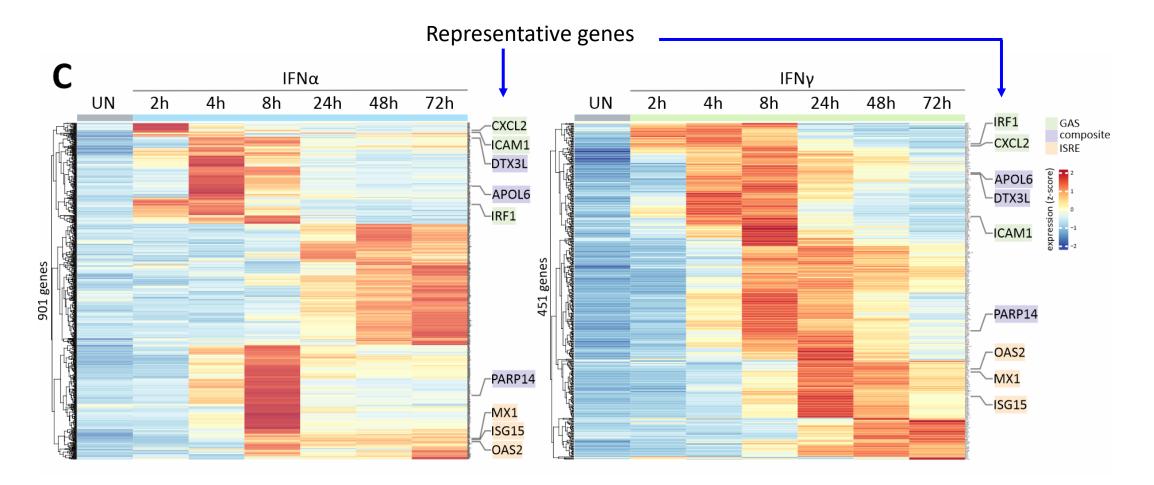


Blencowe B J et al. Genes Dev. 2009;23:1379-1386

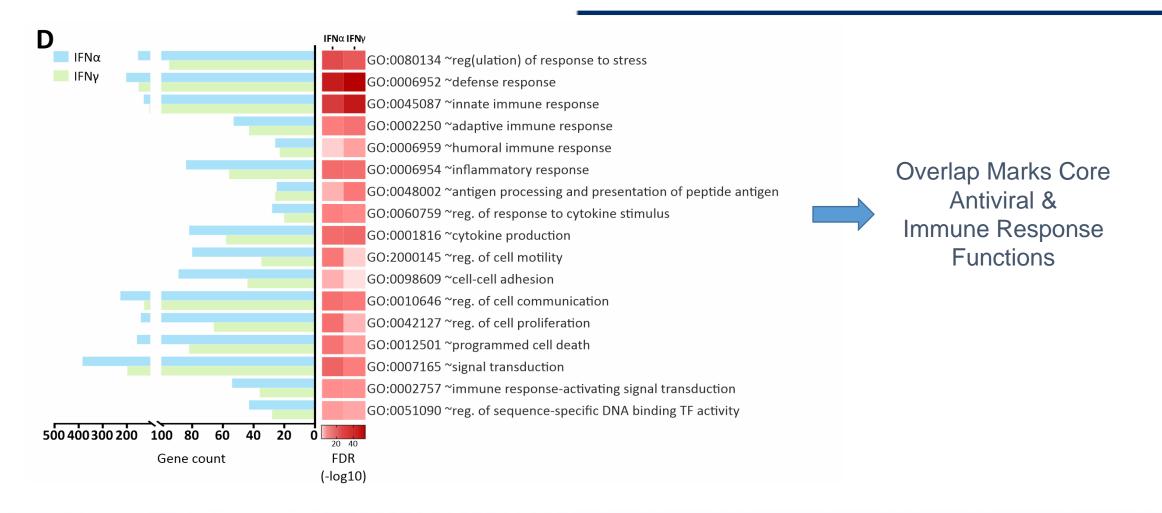
# Genome-wide IFN-I & IFN-II induced Transcription in Time



# Genome-wide IFN-I & IFN-II induced Transcription in Time

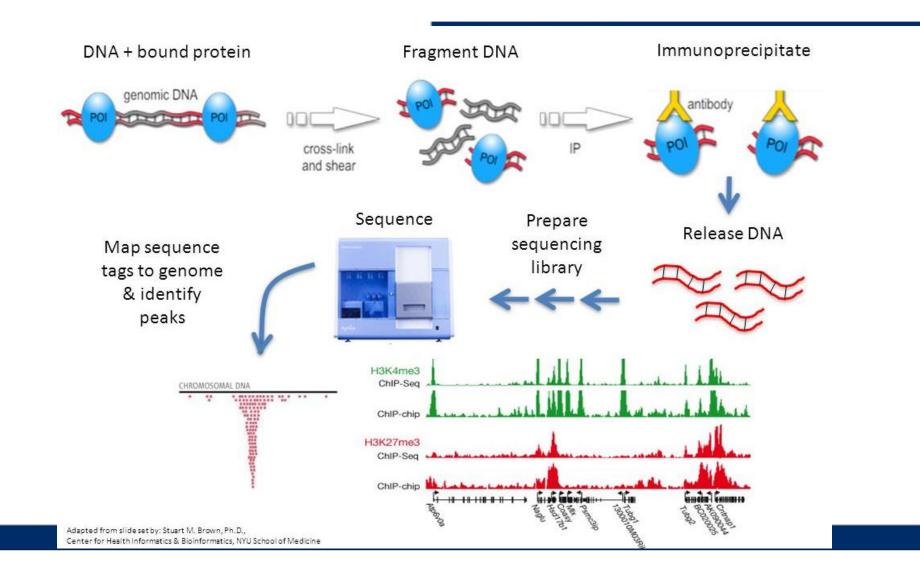


# IFN-I & IFN-II induced Functional Overlap

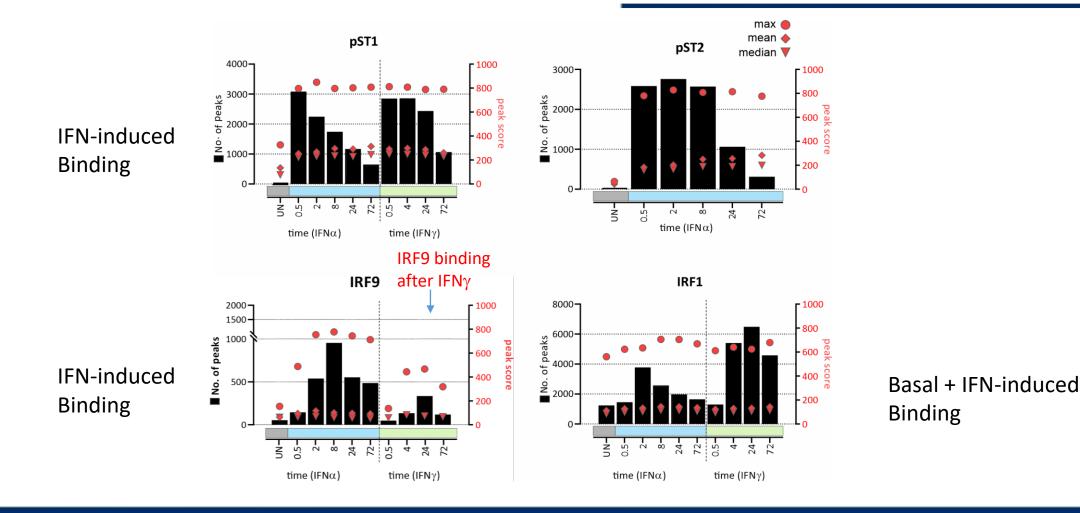


How to analyze chromatin interactions?

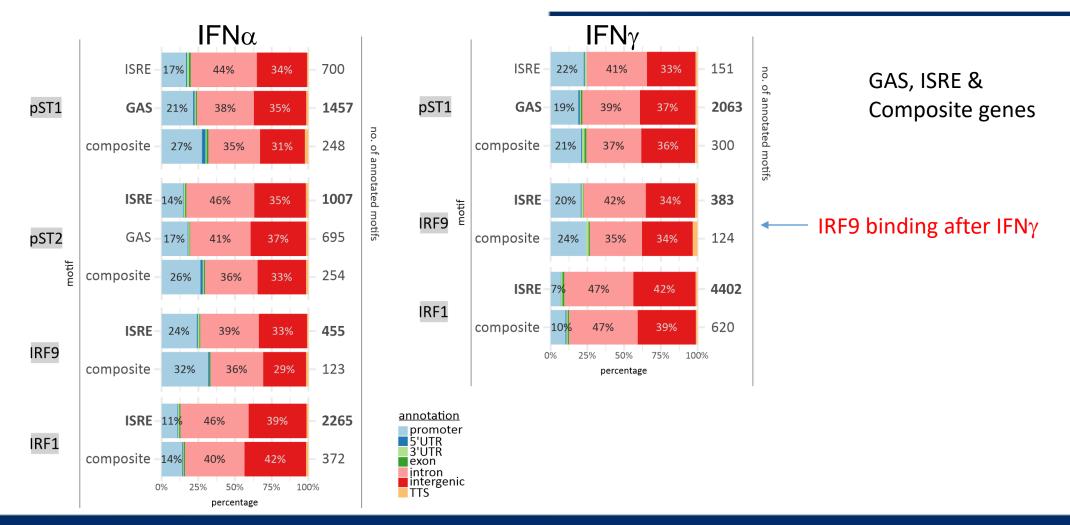
### ChIPseq Workflow

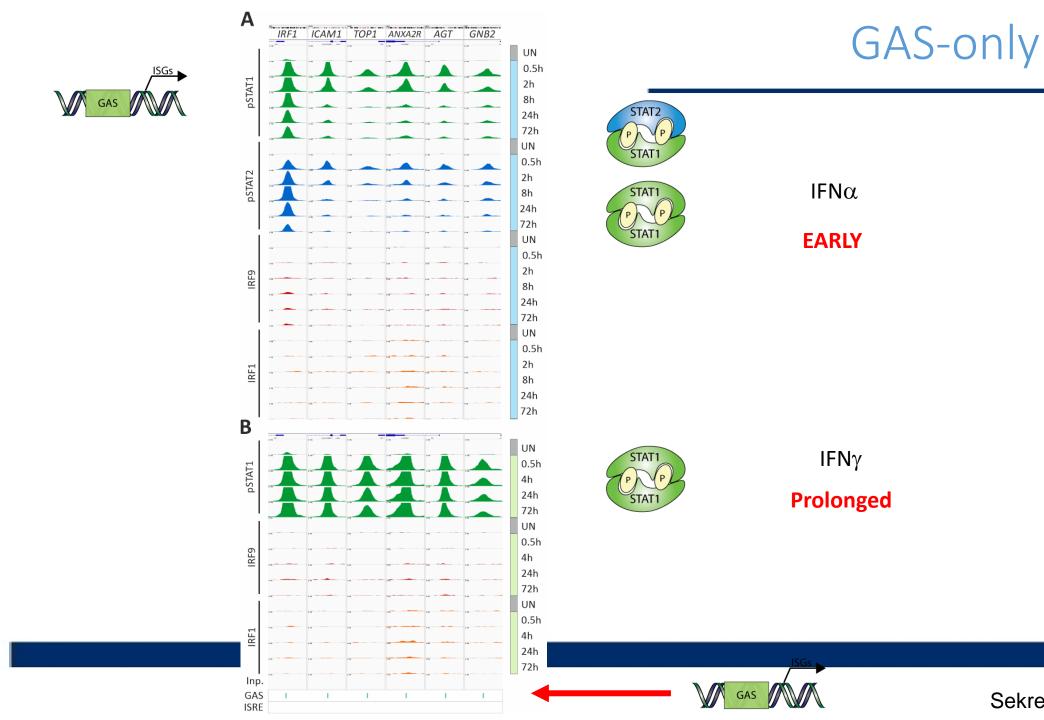


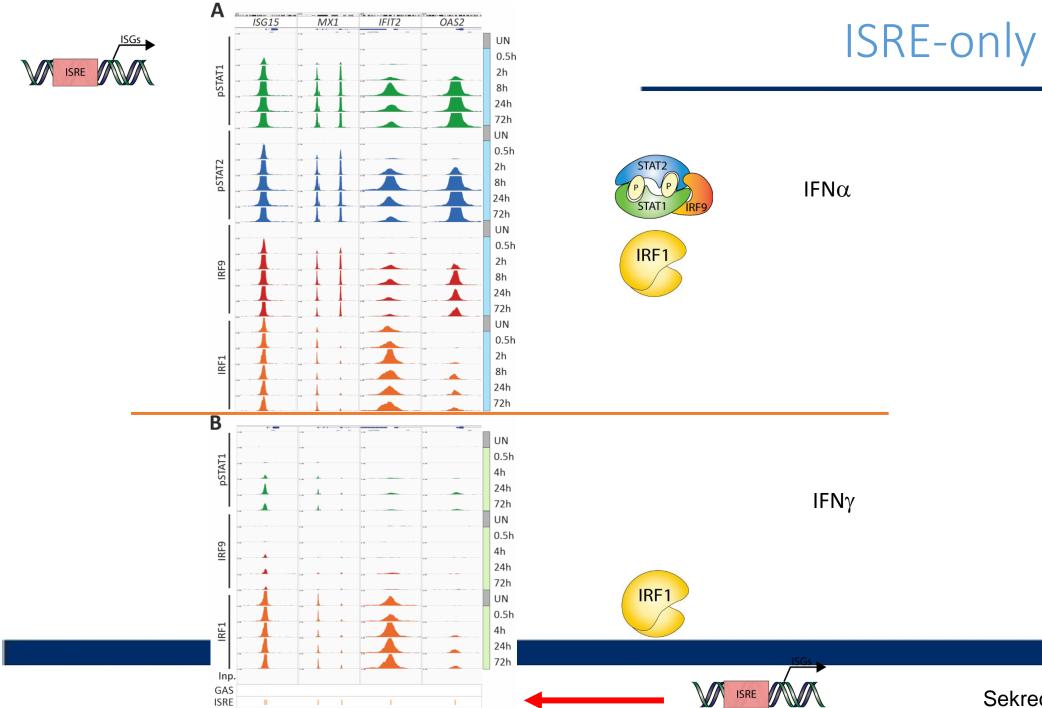
# Genome-wide IFN-I & IFN-II induced Chromatin interactions in Time



# Genome-wide IFN-I & IFN-II induced Chromatin interactions in Time







# Differential complex binding to ISRE and ISRE-GAS Composite genes

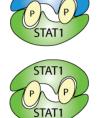
			1	- 11			- 11				uh Wt vs KO			21					1	^	
	chr10	chr2	chr12	chr4	chr9	chr1	chr1	chr1	chr19	chr11	chr1	chr22	chr3	chr7	chr4		chr11	chr2	chr12	chr14	
		0		9			_					5	5	114		6	9	_	N		
	L L	SAD	DAS2	l li	S S	92	IF144L	[5G15	3ST2	BATF2	ADAF	Ę	ARP	MEN I	l õ	4POL	JBE2L6	STAT1	STAT2	E E	
<mark> </mark>			-						11			_			-						
3ene 🛛	IFIT1	RSAD2			6 DDX58	IF16	IFI44L	ISG15	BST2	BATF2	ADAR		PARP9	C7orf49	DDX60	APOL6		TAT1	STAT2	RNF31	
ns HuhWT UN pSTAT1	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	
s_HuhWT_UN_pSTAT2	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	
_HuhWT_UN_IRF9	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	
EHuhWT_UN_IRF1	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	
	🔺 .	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	(0 - 500)	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	(0 - 500)	[0 - 500]	[0 - 500]	
	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	(0 - 300	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]		[0 - 300]	[0 - 300]	
_HuhWT_IFNa_0_5h_IRF9	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200] [0 - 500]	[0 - 200]	STAT2	[0 - 200] 10 - 500]	[0 - 200]	STAT2	[0 - 200]	[0 - 200]	[0 - 200]	. [0 - 292]	[0 - 200]	[0 - 200]	
HuhWT_IFNa_0_5h_IRF1	(0 - 500)	(u - 500)	(u - 500)	(0 - 500)	[0 - 500]	[0 - 500]		[0 - 500]	(u - 500)	0.00		10-300	[0-300]		0- 500j	[0 - 500]		[0 - 500]	[0 - 500]	[0 - 500]	
_HuhWT_IFNa_2h_pSTAT1 HuhWT IFNa 2h pSTAT2	10 - 300	[0 - 300]	10 - 300	[0 - 300]	[0 - 300]	[0 - 300]	10 - 300	10 - 300	[0 - 300]	0		(0 - 300	10-300 P	P/P/		[0 - 300]	IRF1	10-300	[0 - 300]	- 10 - 3001	
HuhWT IFNa 2h IRF9	(0 - 300 (0 - 200		STAT2	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 300] [0 - 200]	(0 - 300) (0 - 200)	[0 - 200]			0 - 200	10-20			[0 - 200]		0-20	[0 - 200]	(0 - 300) (0 - 200)	IFNα
_HuhWT_IFNa_2h_IRF1	[0 - 500]	[0 - 500]			[0 - 500]	-	[0 - 500]	[0 - 500]	[0 - 500]	- IO - V	STAT1	lo - 200	[0 - 500]	STAT1 🦯	IRF9/	[0 - 500]	$\bigcirc$	[0 - 500]	[0 - 500]	[0 - 500]	
HuhWT_IFNa_24h_pSTAT1	(0 - 500	10 - 500 P	A-500 P		[0 - 500]	IRF1	0 - 500	[0 - 500	[0 - 500]	[0 - 500]		lo - 500	[0 - 500]	[0-500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	
HuhWT IFNa 24h pSTAT2	[0 - 300]	10 - 300	NO		[0 - 300]		[0 - 300	(0 - 30 <b>0</b>	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 30]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	
HuhWT_IFNa_24h_IRF9	[0 - 200]	[0 - 200]	STAT1	IRF9/	[0 - 200]		0 - 200)	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	(0 - 200 <b>)</b>	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0-20]	[0 - 200]	[0 - 200]	
_HuhWT_IFNa_24h_IRF1	[0 - 500]	[0 - 500]		[0-500]	[0 - 500]	ln - ami	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	
HuhWT_IFNa_72h_pSTAT1	[0 - 500	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	lo - 200	(0 - 500	[0 - 500]	[0 - 500]	[0 - 500]	<b>[</b> 0 - 500	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	
_HuhWT_IFNa_72h_pSTAT2															<b></b>	<b>.</b>			1.	<b>.</b>	
_HuhWT_IFNa_72h_IRF9	(0 - 200)	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	(0 - 200)	[0 - 200]	[0 - 200]	[0 - 200]	(0 - 200	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0-20]	[0 - 200]	[0 - 200]	
HuhWT_IFNa_72h_IRF1	[0 - 500]	[0 - 500]	[0 - 500] [0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500] [0 - 500]	(o - 600)	[0 - 500]	[0 - 500]	[0 - 500]	(0 - 500)	[0 - 500]	[0 - 500]	[0 - 500]	(0 - 500)	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	
HuhWT_IFNy_0_5h_pSTAT1	[0 - 500]	(0 - 100)	[0 - 100]	[0 - 100]	[0 - 300]	[0 - 500]	[0 - 100]	[0 - 500]	(0 - 500) (0 - 100)	[0 - 100]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 100]	[0 - 100]	[0 - 500] [0 - 100]	[0 - 500]	[0 - 500]	
_HuhWT_IFNy_0_5h_STAT2 HuhWT IFNy 0 5h IRF9	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 100]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 100]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 100]	
HuhWT_IFNy_0_5h_IRF1	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	
_HuhWT_IFNy_4h_pSTAT1	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	(0 - 500)	CTAT1	lo - 200	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	P	500	[0 - 500]	[0 - 500]	
HuhWT_IFNy_4h_STAT2	[0 - 100]	[0 - 100]	[0 - 100]	-	[0 - 100]	[0 - 100]	[0 - 100]	[0 - 100]	[0 - 100]	[0 - 100]	STAT1	. 100	[0 - 100]	i 🦳	i n	[0 - 100]	STAT1		[0 - 100]	[0 - 100]	
HuhWT_IFNy_4h_IRF9		-		IRF1		<b>.</b>					P		1	IRF1							
HuhWT_IFNy_4h_IRF1	[0 - 500]	[0 - 500]	(0 - 500)		[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500			[0 - 500]			[0 - 500]	PAY	PK	[0 - 500]	[0 - 500]	
_HuhWT_IFNy_24h_pSTAT1	[0 - 500]	[0 - 500]	[0 - 500]		[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	STAT1	IRF9	[0 - 500]	I (	n T	[0 - 500]	STAT1		[0 - 500]	[0 - 500]	
HuhWT_IFNy_24h_STAT2	[0 - 100]	[0 - 100]	[0 - 100]	10-100j	[0 - 100]	[0 - 100]	[0 - 100]	[0 - 100]	[0 - 100]	[0 - 100]			[0 - 100]	1	<sup>20</sup>	[0 - 100]	SIAH	100	[0 - 100]	[0 - 100]	IFNγ
HuhWT_IFNy_24h_IRF9	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	(0 - 200 <b>0</b>	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	11 1 1 1
_HuhWT_IFNy_24h_IRF1	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	(0 - 500)	lo - 2001	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	
_HuhWT_IFNy_72h_pSTAT1	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	10 - 500	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 500]	[0 - 590] [0 - 100]	[0 - 500]	(0 - 500)	
_HuhWT_IFNy_72h_STAT2	[0 - 100]	[0 - 100]	[0 - 100]	[0 - 100]	[0 - 100]	[0 - 100]	[0 - 100]	[0 - 100]	[0 - 100] [0 - 200]	[0 - 100]	[0 - 100]	[0 - 100]	[0 - 100]	[0 - 100]	[0 - 100]	[0 - 100]	[0 - 100]	[0 - 100]	[0 - 100]	[0 - 100]	
_HuhWT_IFNy_72h_IRF9 _HuhWT_IFNy_72h_IRF1	[0 * 200]	(0 · 200)	[0 · 200]	- 200	10 - 2001	10 · 200]	[0 · 200]	[0 - 200]	[0 · 200]	10 · 200j	[0 - 200]	[0 - 200]	[0 · 200]	[0 * 200]	[0 * 200]	[5 - 200]	(o - 200)	[0 - 200]	10 · 200j	10 ° 200j	
_HUNVVI_IENV_/2N_IRE1	<b></b>													<b>_</b>				1. 1.		×	

ISRE

GAS

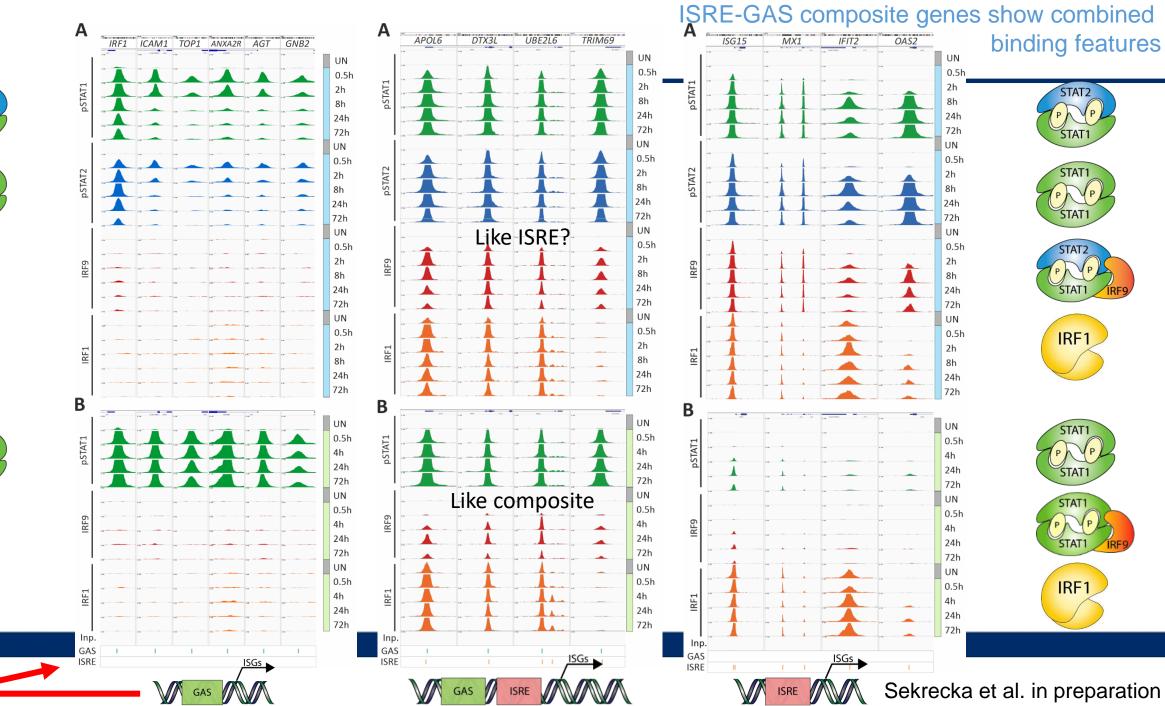
ISRE

eannei

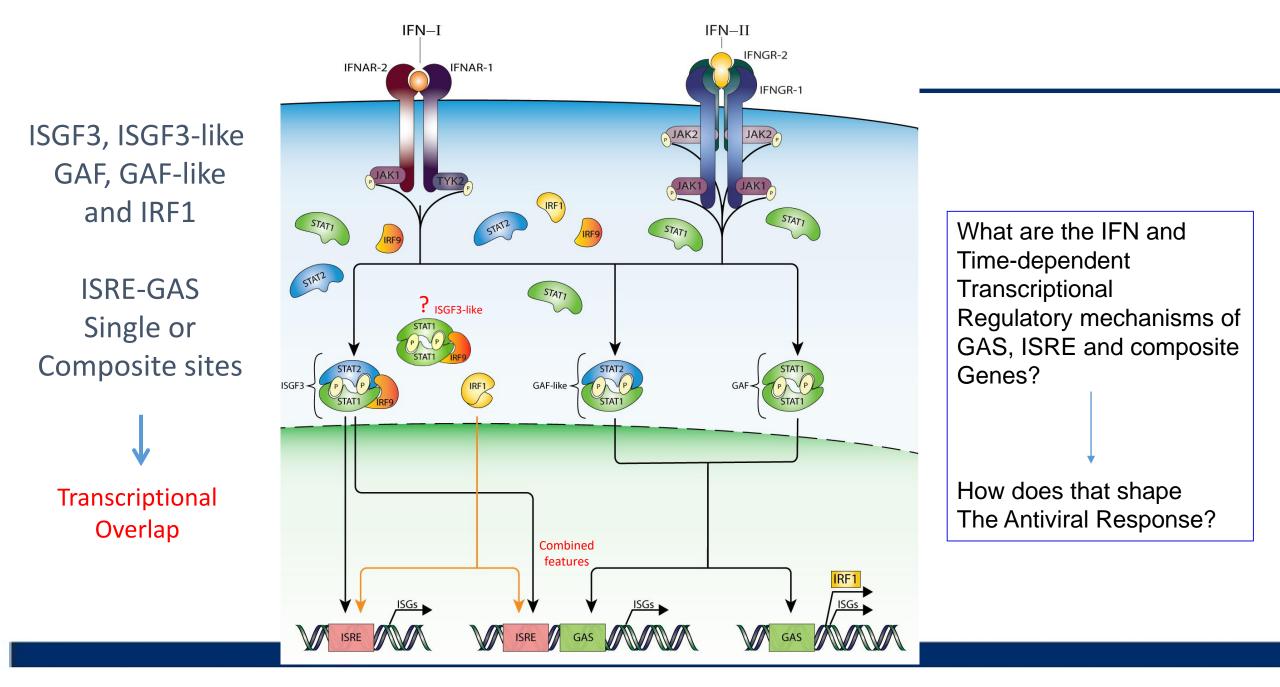


STAT2



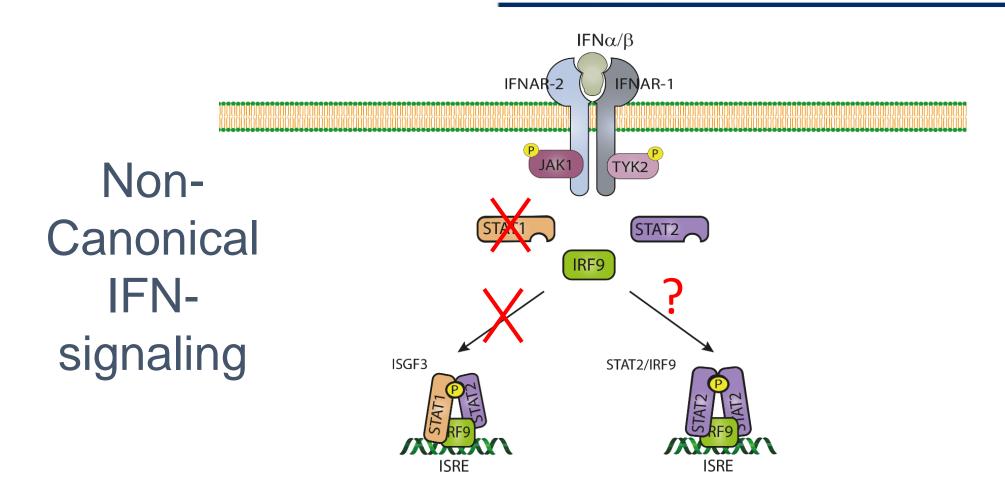


TAT



Michalska et al. 2018, Frontiers in Immunology

### Alternative IFN-I-signaling in the absence of STAT1



Bluyssen, Oncotarget 2015

### Alternative complexes: IFN-I-signaling in the absence of STAT1



Bluyssen HAR & Levy DE JBC 1997

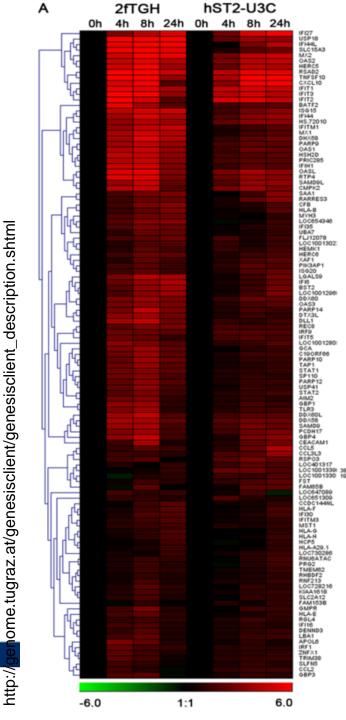






Yamauchi et al., Scientific Rep 2016

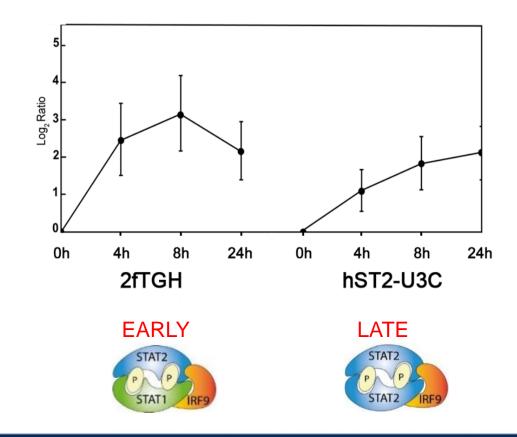
Michalska et al.



# IFN-I Signaling: ISGF3 vs STAT2/IRF9

**Genome-wide characterization** 

**Commonly up-regulated ISGs** 



Blaszczyk et al., Biochem J, 2015

### STAT2/IRF9 binds classical ISRE-containing ISGs

ChIP	ISRE-Motif	p-value	%Target	%Background
IRF9 2h IRF9 24h	AGTTTCAGTTIC II	1e-161 1e-240	38.79% 34.53%	0.30% 0.34%
STAT2 24h	<sub>∼ ee</sub> tttc, ∏I₂e	1e-71	26.89%	0.95%



Blaszczyk et al., 2017



#### STAT1KO: IFNα Switch to ISRE-only + Prolonged response

OAS2

TRIM69

UN 2h

> 24h 72h

UN 2h

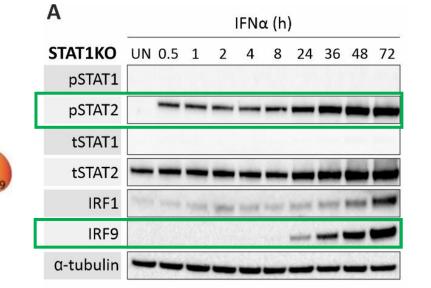
24h 72h

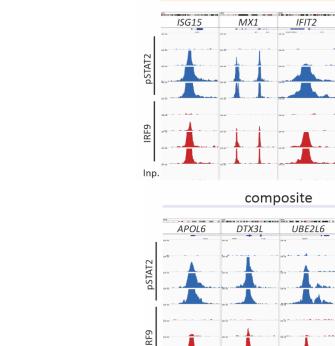
UN

2h 24h 72h UN 2h

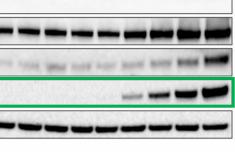
24h 72h

ISRE





Inp.









In the absence of STAT1, STAT2/IRF9 takes over the role of ISGF3

Huh7.5-STAT1KO



Bluyssen et al. 1997; Blaszczyk et al. 2015

# IFN-I Signaling: ISGF3 vs STAT2/IRF9

	chr12	chr10	chr1	chr21	chr12	chr3	chr3	chr22	chr3	chr17	chr2	chr20	chr9	chr17	chr1
	0AS2	ILII	ISG15	MXI	OA53	PARP14	PARP9	APOL6	DTX3L	GP	EIF2AK2	ZNFX1	TRIM14	RNF213	IF16
Gene			ISG15	MX1			1 1 PARP9			-r -	CIEIF2AK2	NFX1			S IFI6
hs_HuhWT_UN_pSTAT1	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0-300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]
hs_HuhWT_UN_IRF9	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]
hs_HuhWT_UN_pSTAT2	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]
hs_HuhWT_IFNa_2h_pSTA1	[0 - 300]	[0 - 300]	[0 - 309	(0 - 300)	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 399]	[0 - 300]	[0 - 300]	[0 - 300]
hs_HuhWT_IFNa_2h_pSTA1∠	[0 - 300]	[0 - 300]	[0 - 309]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	(0 - 300)	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]
hs_HuhWT_IFNa_2h_IRF9	[0 - 200]	[0 - 200	[0 - 202]	Į0 - 200	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]
hs_HuhWT_IFNa_24h_pSTAT1	[0 - 300]	[0 - 302]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300],	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 309]	[0 - 300]
hs_HuhWT_IFNa_24h_pSTAT2	[0 - 300]	[0 - 302]	[0 - 300]	(0 - 30Q)	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 309]	[0 - 300]
hs_HuhWT_IFNa_24h_IRF9	[0 - 200]	[0 - 200	[0 - 200 <b>1</b>	[0 - 200	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]
hs_HuhWT_IFNa_72h_pSTAT1	[0 - 300]	[0 - 302]	[0 - 300]	Į0 - 300	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 3 <b>00</b> ]	[0 - 300]	[0 - 300]	[0 - 300]
hs_HuhWT_IFNa_72h_pSTAT2	[0 - 300]	[0 - 302]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	(0 - 3 <b>90</b> )	[0 - 300]	(0 - 300)	[0 - 300]
hs_HuhWT_IFNa_72h_IRF9	[0 - 200]	[0 - 200]	[0 - 202	[0 - 200	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]
hs_HuhST1KO_UN_pSTAT2	[0 - 300]	[0 - 300]	[0 - 300]	fo - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	(o - 300)	[0 - 300]	[0 - 300]	0 - 300)	[0 - 300]	[0 - 300]	[0 - 300]
hs_HuhST1KO_UN_IRF9	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]
hs_HuhST1KO_IFNa_2h_pSTAT2	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]
hs_HuhST1KO_IFNa_2h_IRF9	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]
hs_HuhST1KO_IFNa_24h_pSTAT2	[0 - 300]	[0 - 300]	[0 - 300]	(0 - 300)	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 309]	[0 - 300]
hs_HuhST1KO_IFNa_24h_IRF9	[0 - 200]	[0 - 200	[0 - 20 <del>0]</del>	[0 - 200	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200	[0 - 200]	[0 - 209]	[0 - 200]
hs_HuhST1KO_IFNa_72h_pSTAT2	[0 - 300]	lo - 300	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 300]	[0 - 3 <b>90</b> ]	[0 - 300]	[0 - 309]	[0 - 300]
hs_HuhST1KO_IFNa_72h_IRF9	[0 - 200]	[0 - 200]	[0 - 202]	[0 - 200	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 200]	[0 - 299]	[0 - 200]	[0 - 200]	[0 - 200]



ISGF3: EARLY

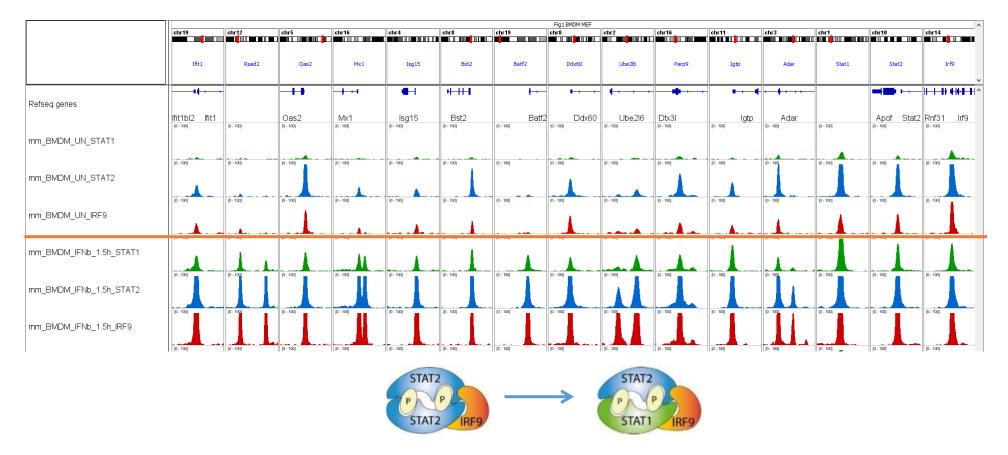


STAT2/IRF9: LATE

Michalska et al.

### Mouse BMDM

#### STAT2/IRF9: basal binding! ISGF3: upon IFN-I

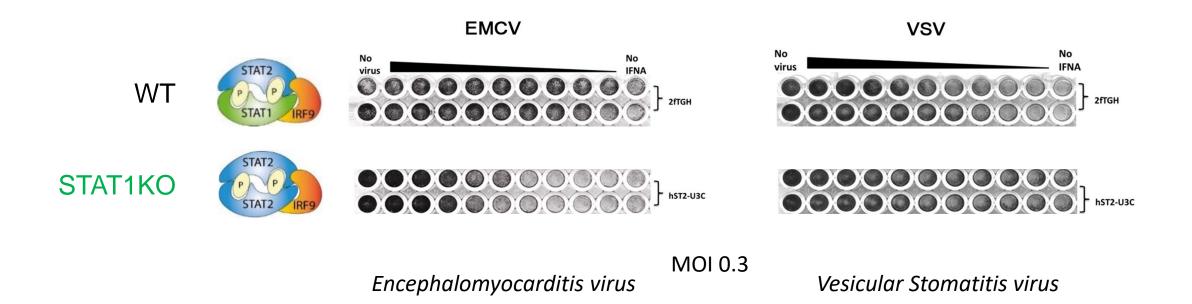


Decker et al. 2019

Michalska et al. 2019

### STAT2/IRF9 Reconstitutes IFN-I-mediated Anti-viral responses

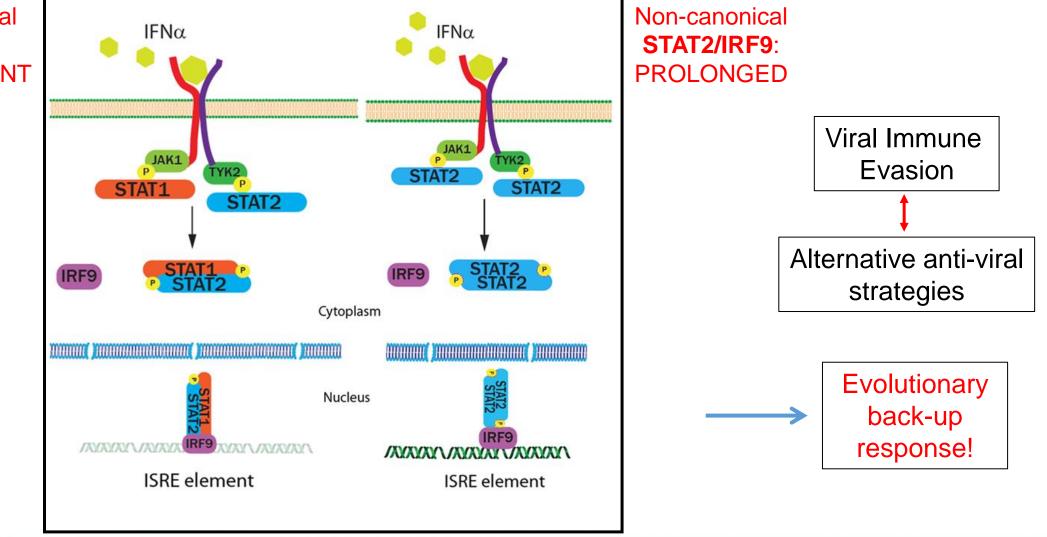
#### **Biological Function!**



Blaszczyk et al., Biochem J, 2015

### STAT2/IRF9 Reconstitutes IFN-I-mediated responses

Canonical ISGF3: TRANSIENT



Blaszczyk et al., CGFR, 2016

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