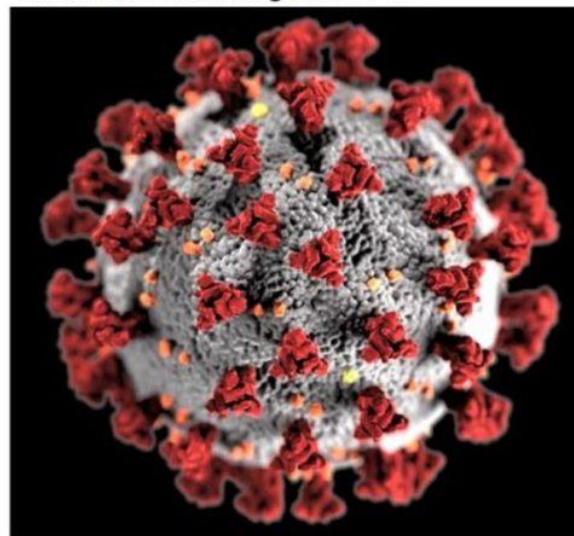
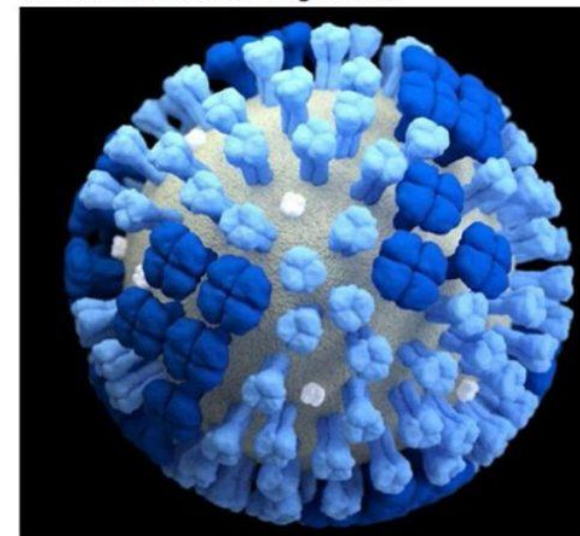


Time-dependent IFN-induced Chromatin Interactions & Gene Transcription Shape the Antiviral Response

SARS-CoV-2 causing COVID-19

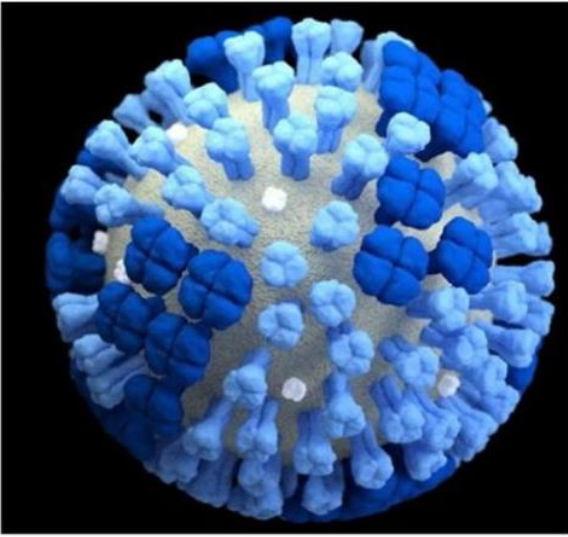


Influenza virus causing the flu

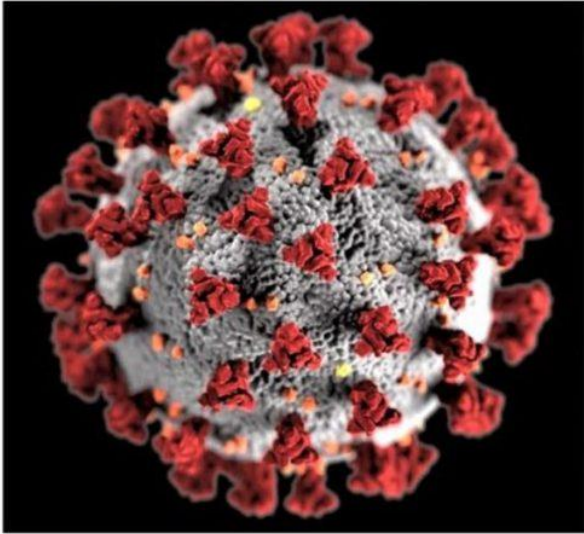


Hans Bluyssen, 21.01.2022

Influenza virus causing the flu



SARS-CoV-2 causing COVID-19

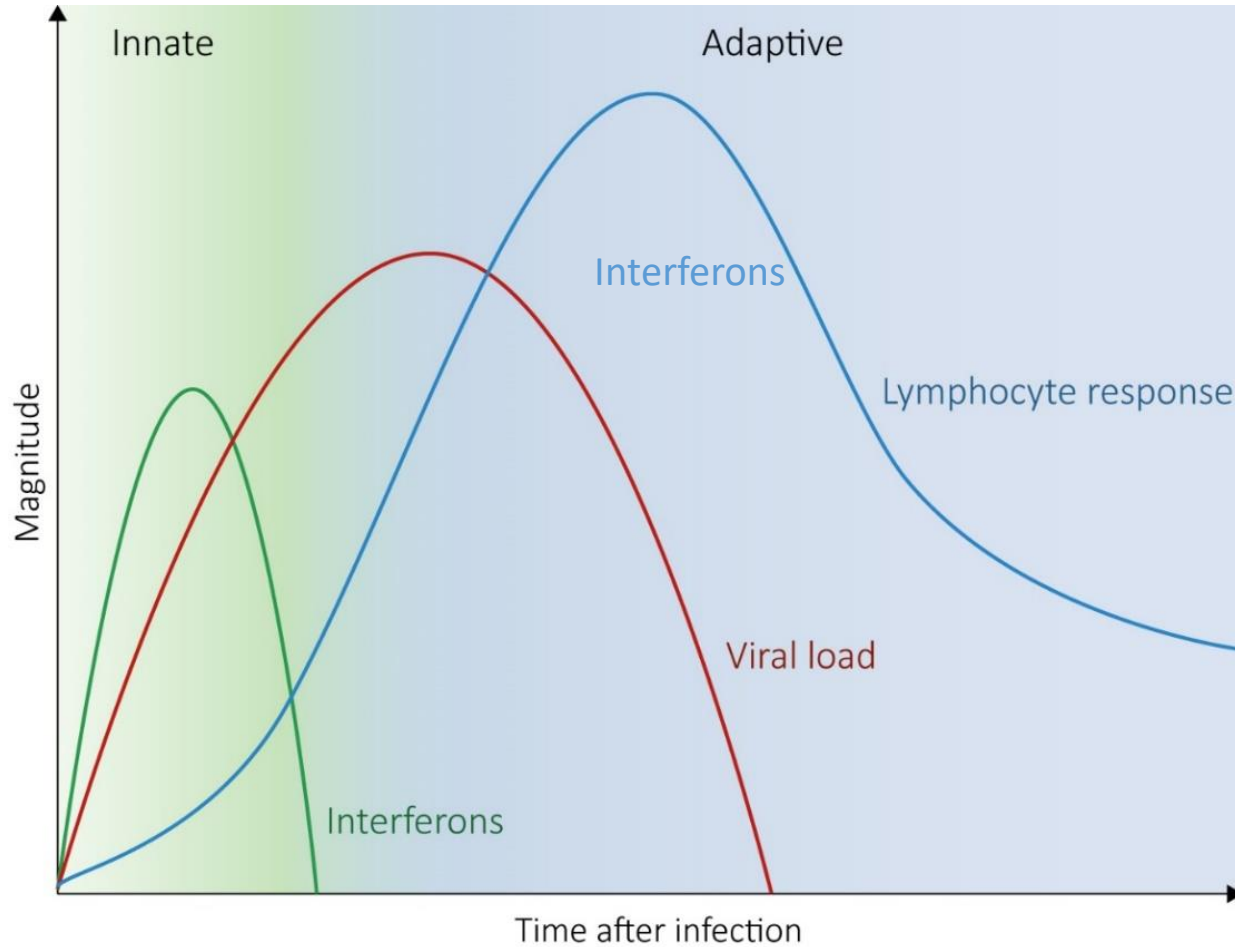


Viral Infection



**What is
happening?**

Anti-viral Response & IFNs



Nature Reviews | Immunology





Anti-viral Response & IFNs

Interferons (IFNs) are released by [host cells](#) in response to the presence of many [viruses](#) causing nearby [cells](#) to heighten their anti-viral defenses.

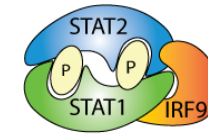
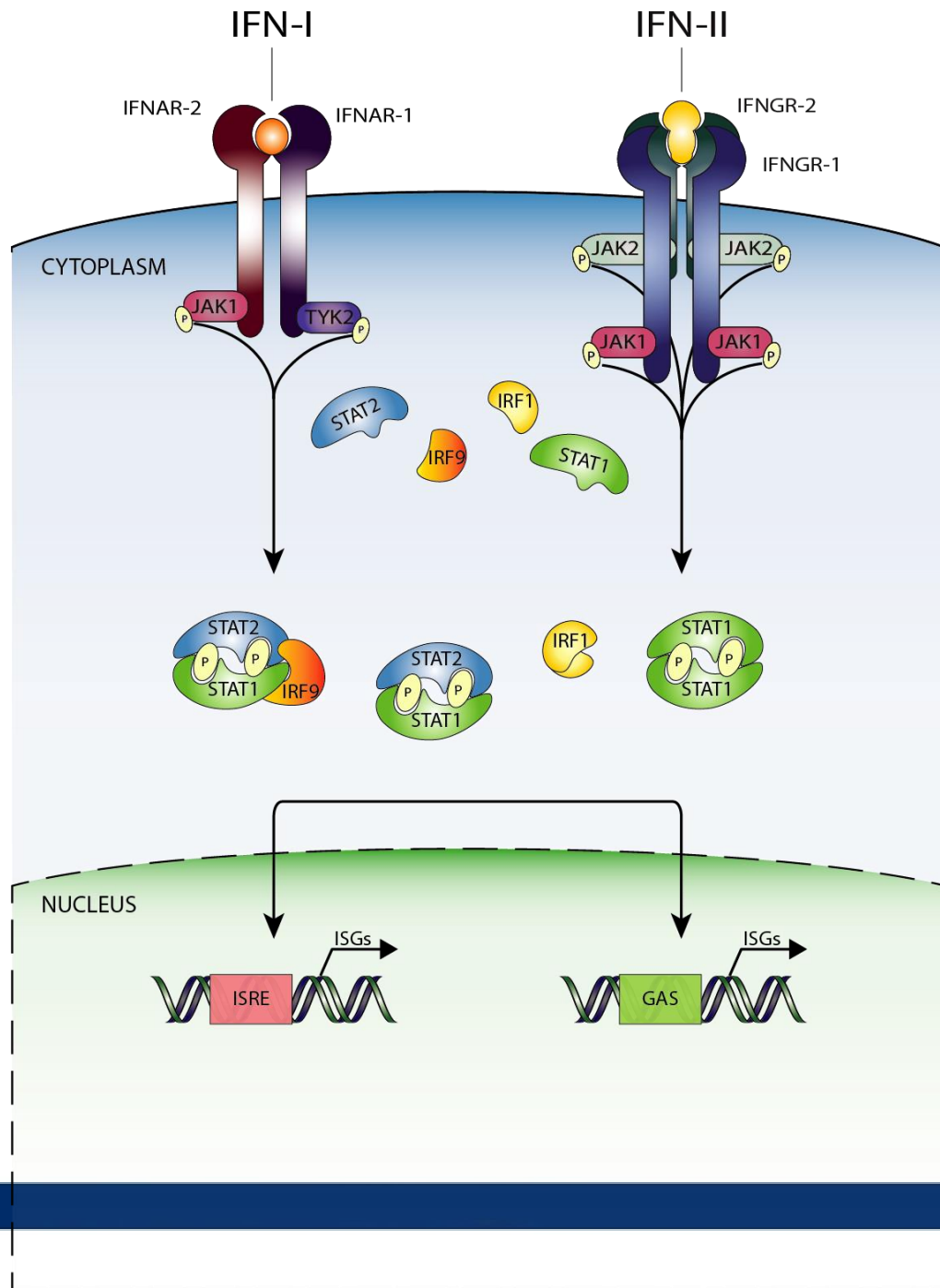
IFNs belong to the large class of [proteins](#) known as [cytokines](#), molecules used for communication between cells to trigger the protective defenses of the [immune system](#) that help eradicate pathogens.

IFNs are named for their ability to "interfere" with [viral replication](#)^[3] by protecting cells from [virus infections](#).

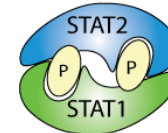
IFNs also have various other functions: they activate [immune cells](#), such as [natural killer cells](#) and [macrophages](#); they increase host defenses by up-regulating [antigen presentation](#) by virtue of increasing the expression of [major histocompatibility complex](#) (MHC) [antigens](#).

Certain symptoms of infections, such as [fever](#), [muscle pain](#) and "flu-like symptoms", are also caused by the production of **IFNs** and other [cytokines](#).

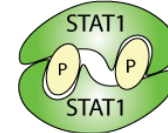
IFN-I & IFN-II induced Signaling & Transcription



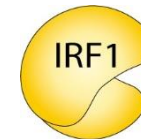
ISGF3



GAF-like

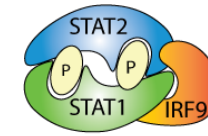
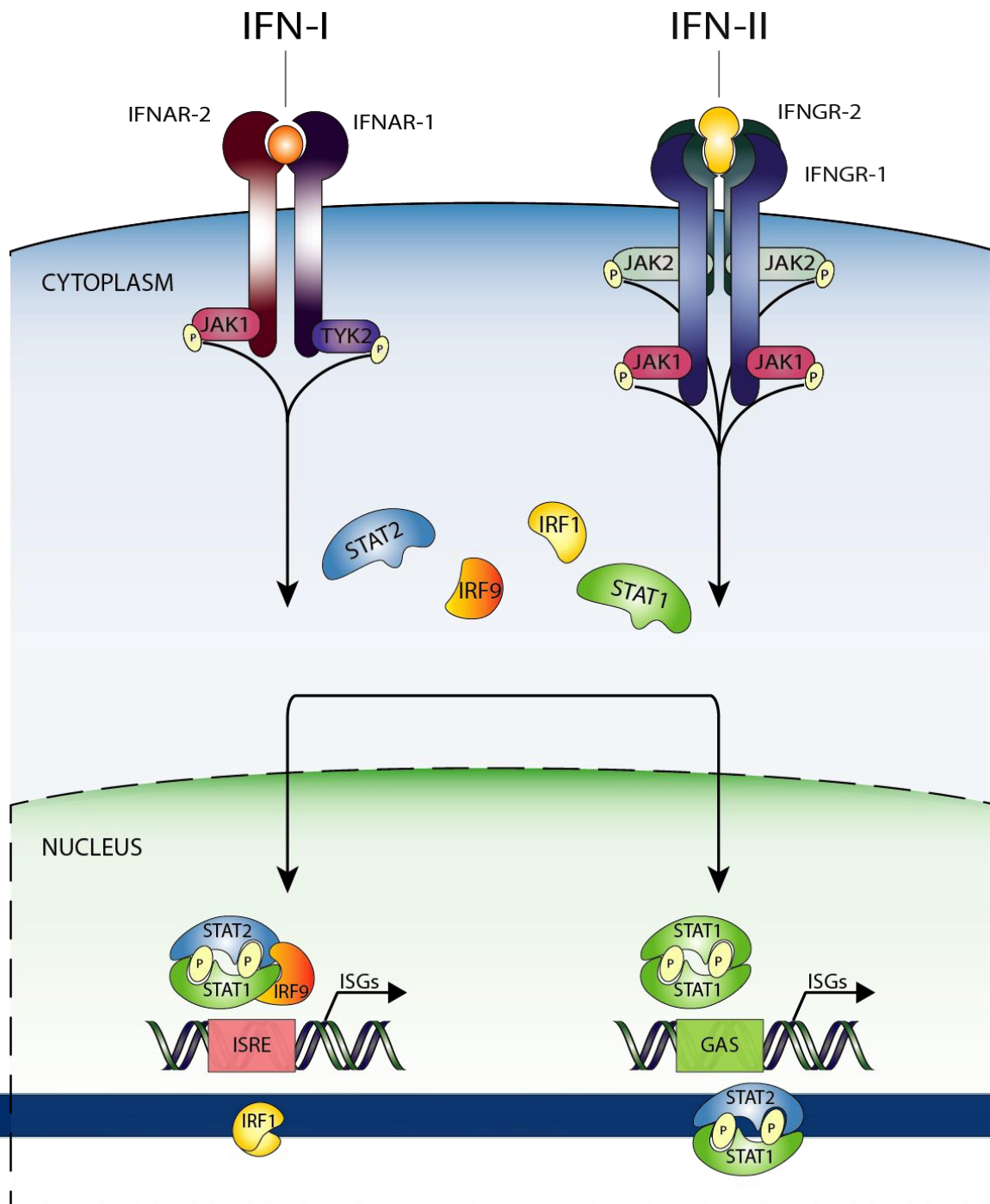


GAF

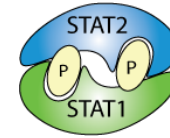


IRF1

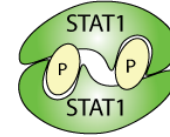
IFN-I & IFN-II induced Signaling & Transcription



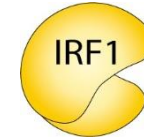
ISGF3



GAF-like



GAF

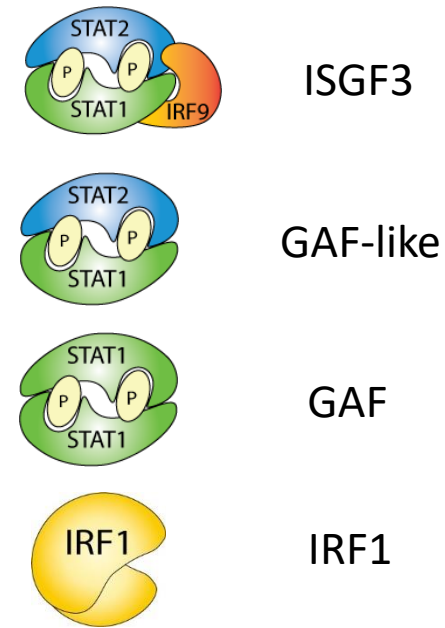
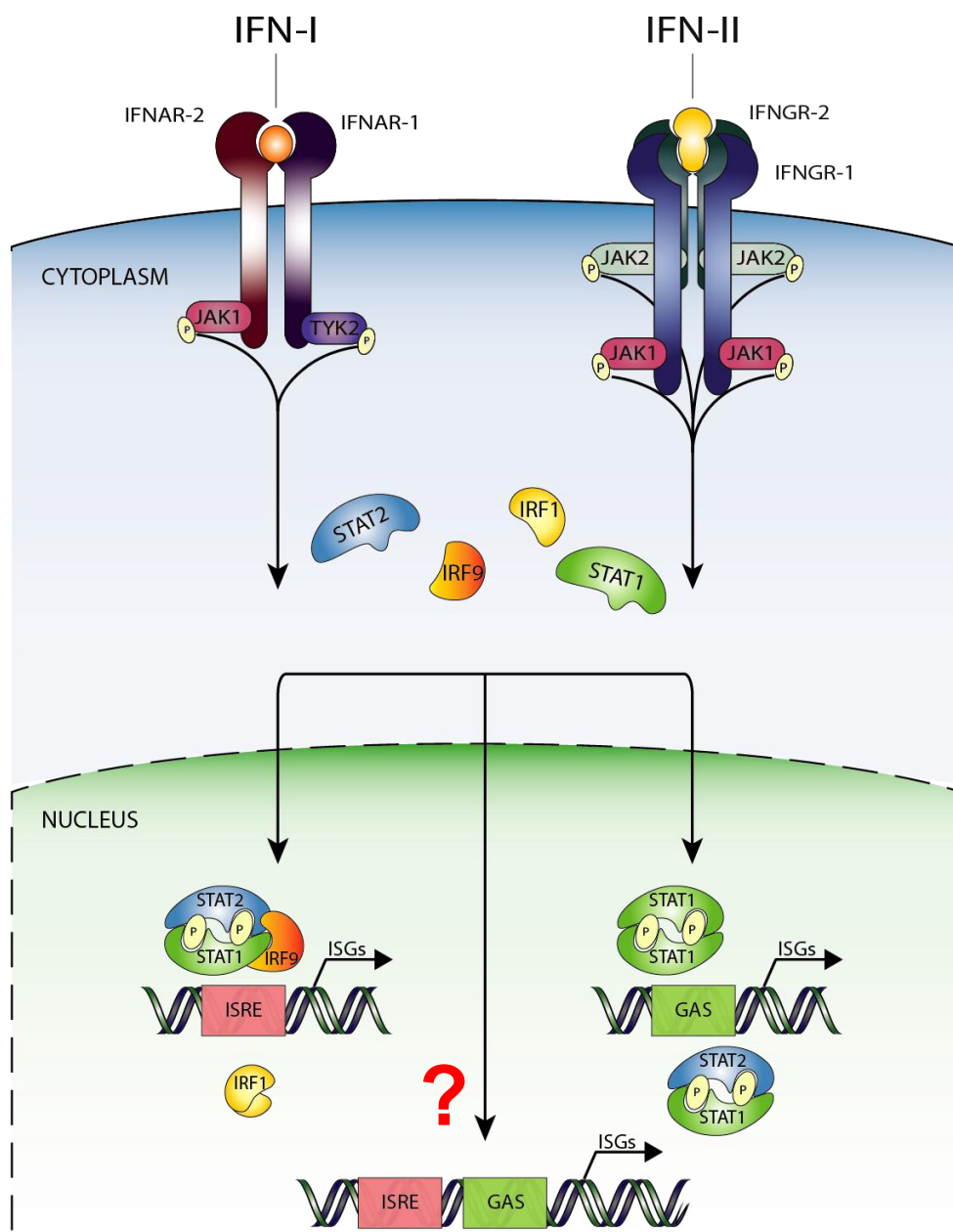


IRF1

Mechanistic Overlap
explains
Functional Overlap

Anti-Viral Response

IFN-I & IFN-II induced Signaling & Transcription

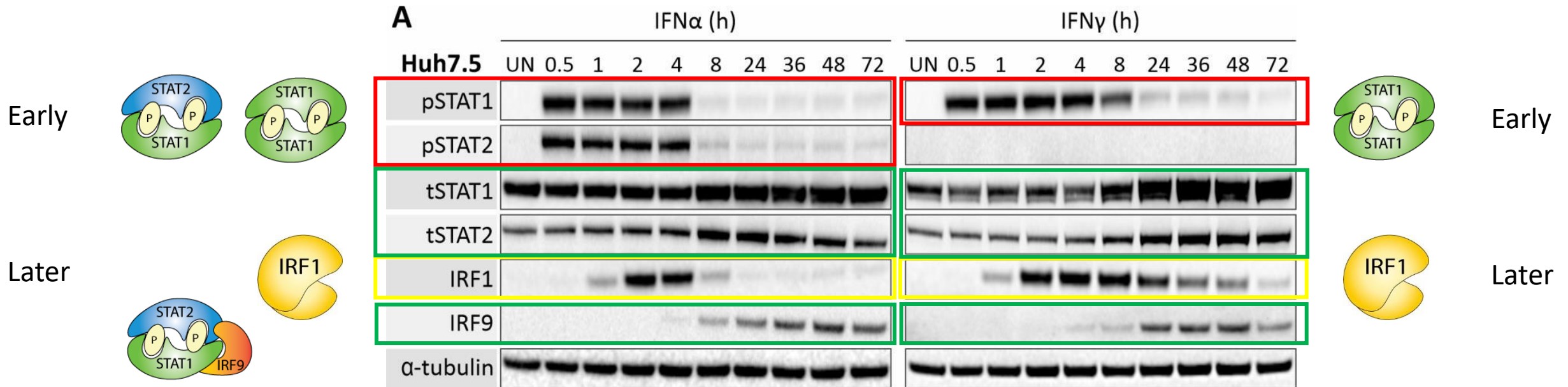


Understand in detail
Mechanistic Overlap

-Transcriptional response
-Chromatin interactions
-Biology

Anti-Viral Response

IFN-signaling In Time: pSTAT1, pSTAT2, IRF9 & IRF1

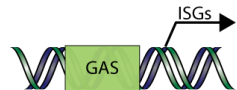
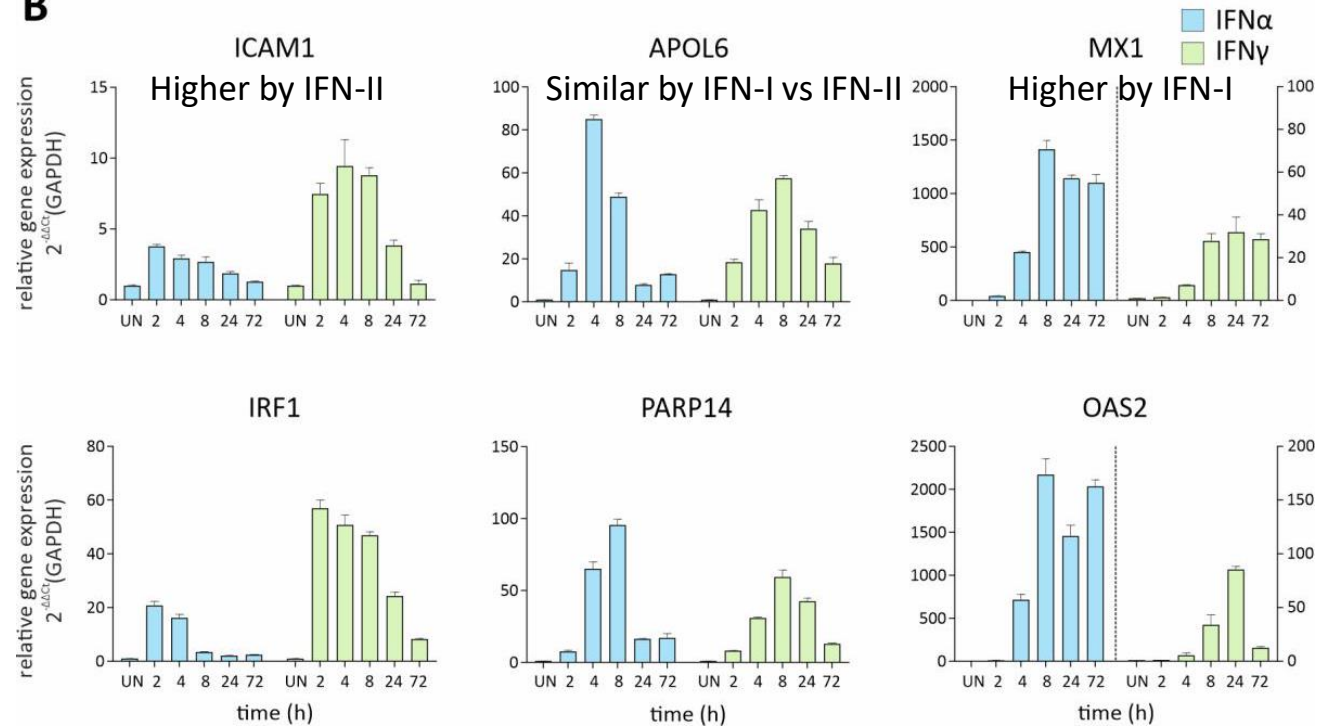


Common signaling mechanisms

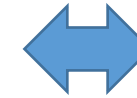
IFN-I & IFN-II induced Transcriptional Response in Time

Representative genes

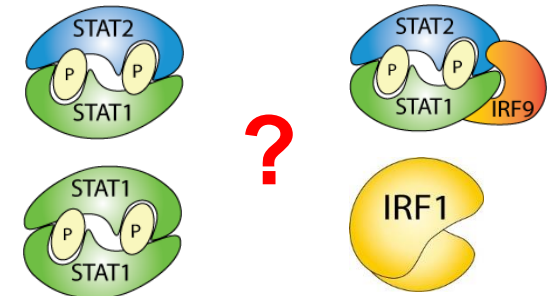
B



Overlapping gene expression



Complex formation



Chromatin Interactions

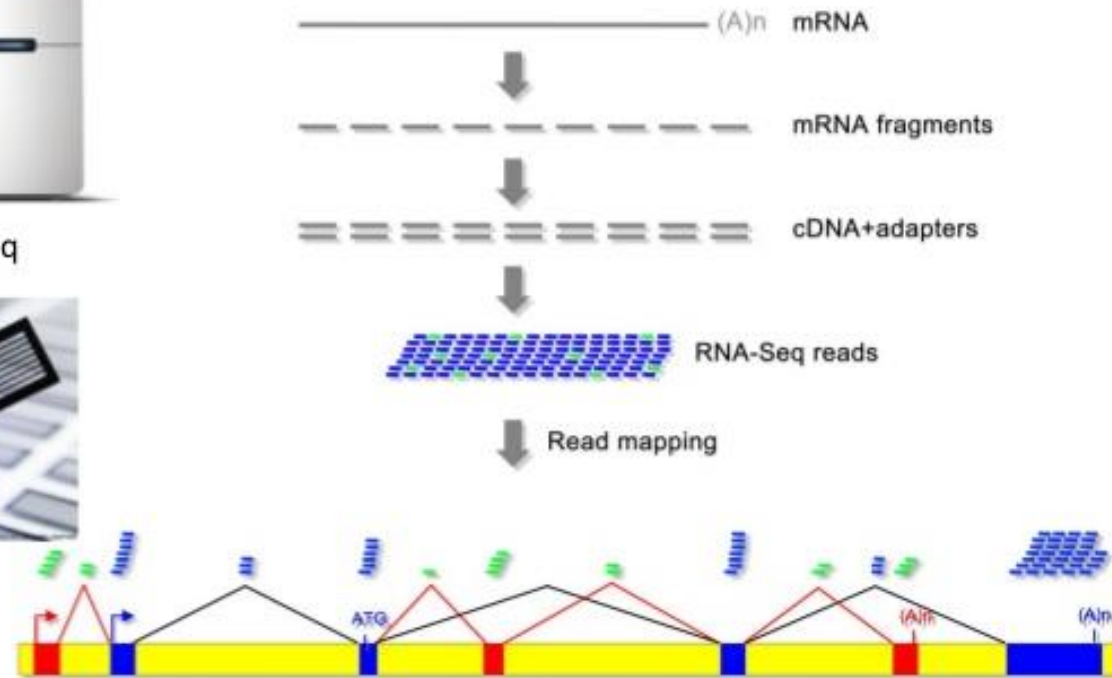
Genome-wide?

How to analyze the
transcriptome?

RNA-seq Work Flow

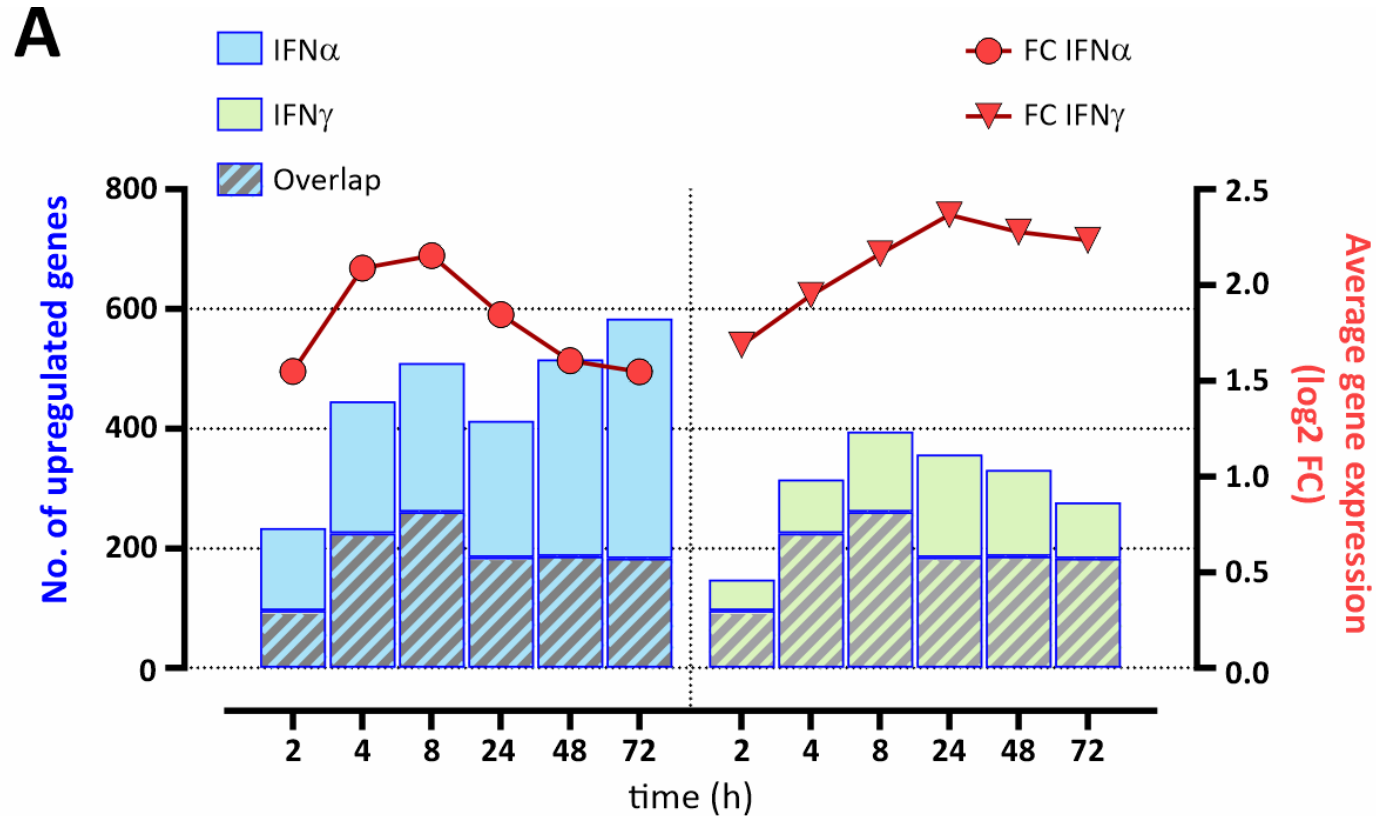


Illumina HiSeq



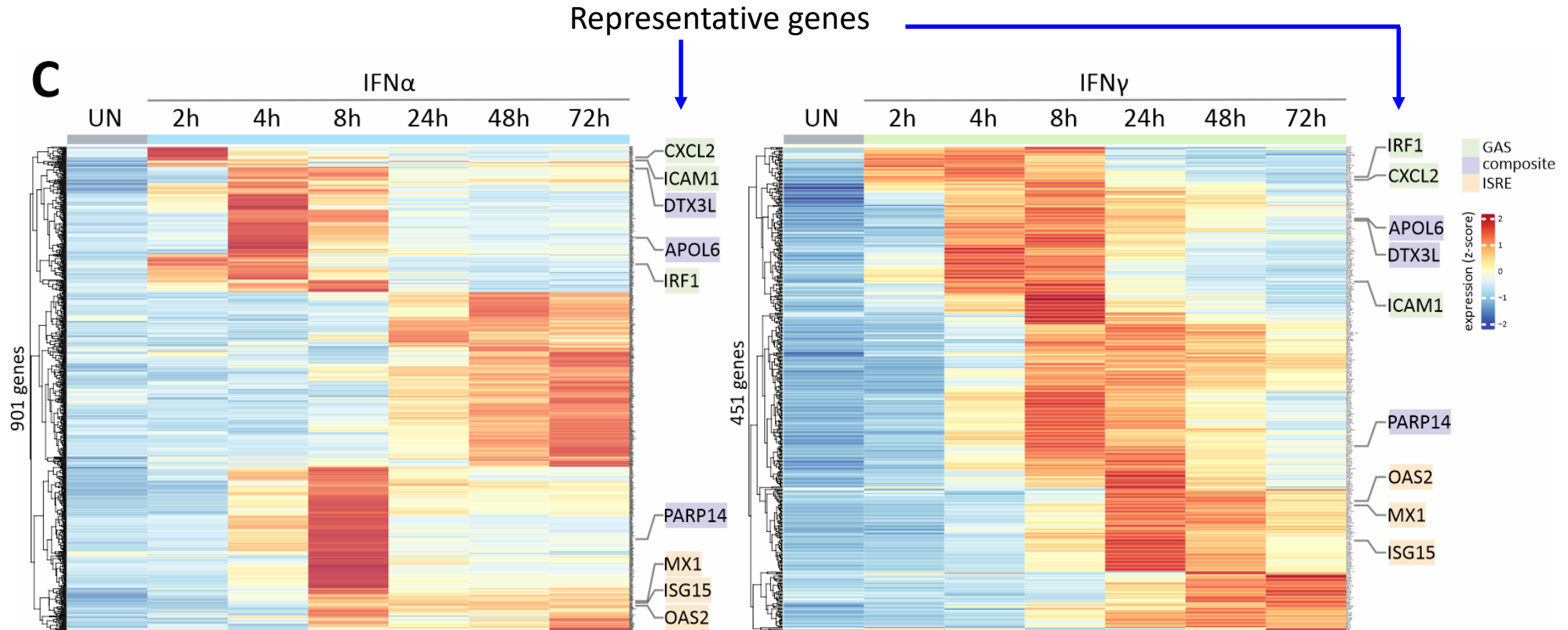
Blencowe B J et al. Genes Dev. 2009;23:1379-1386

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

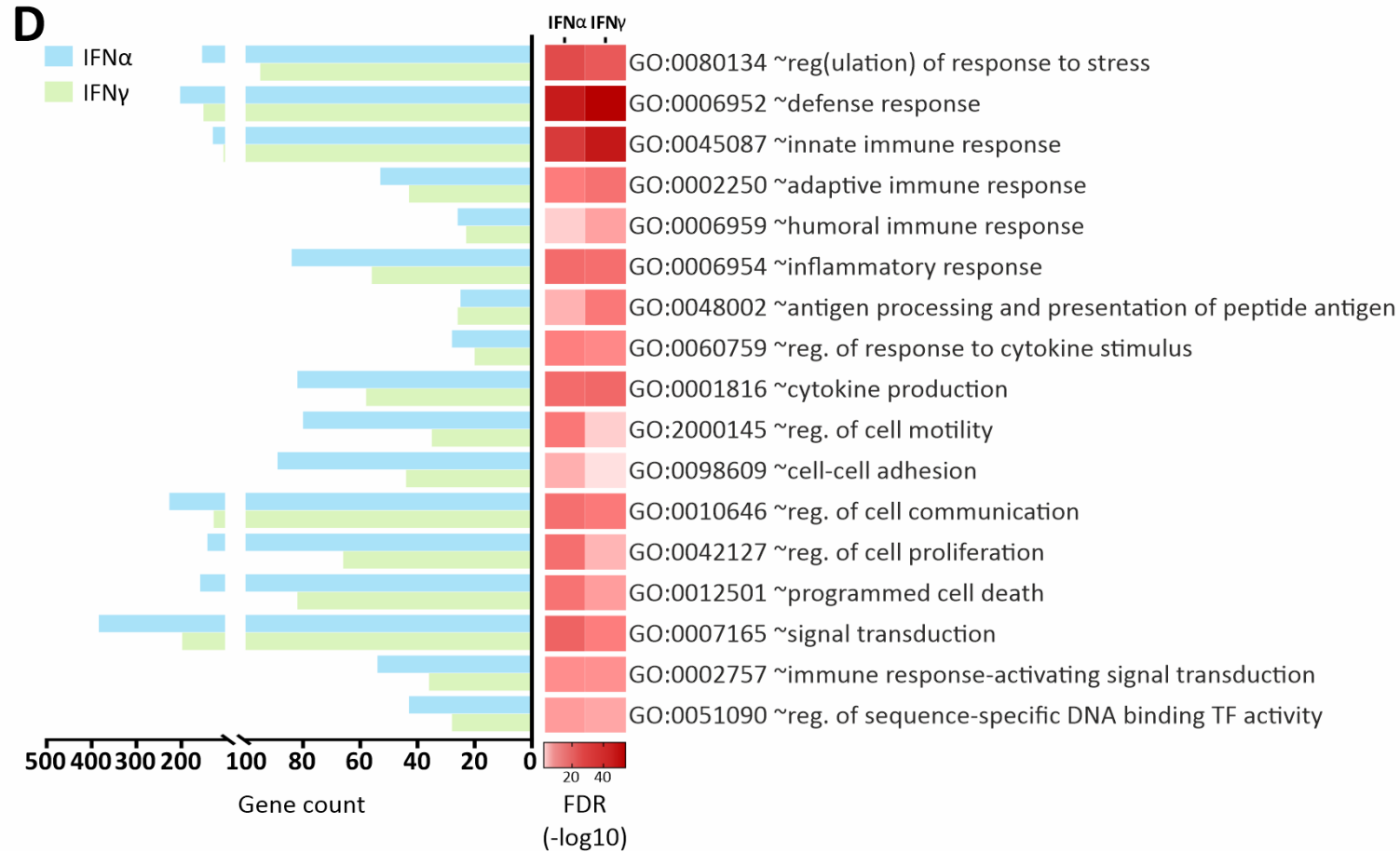


Mechanistic Overlap

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



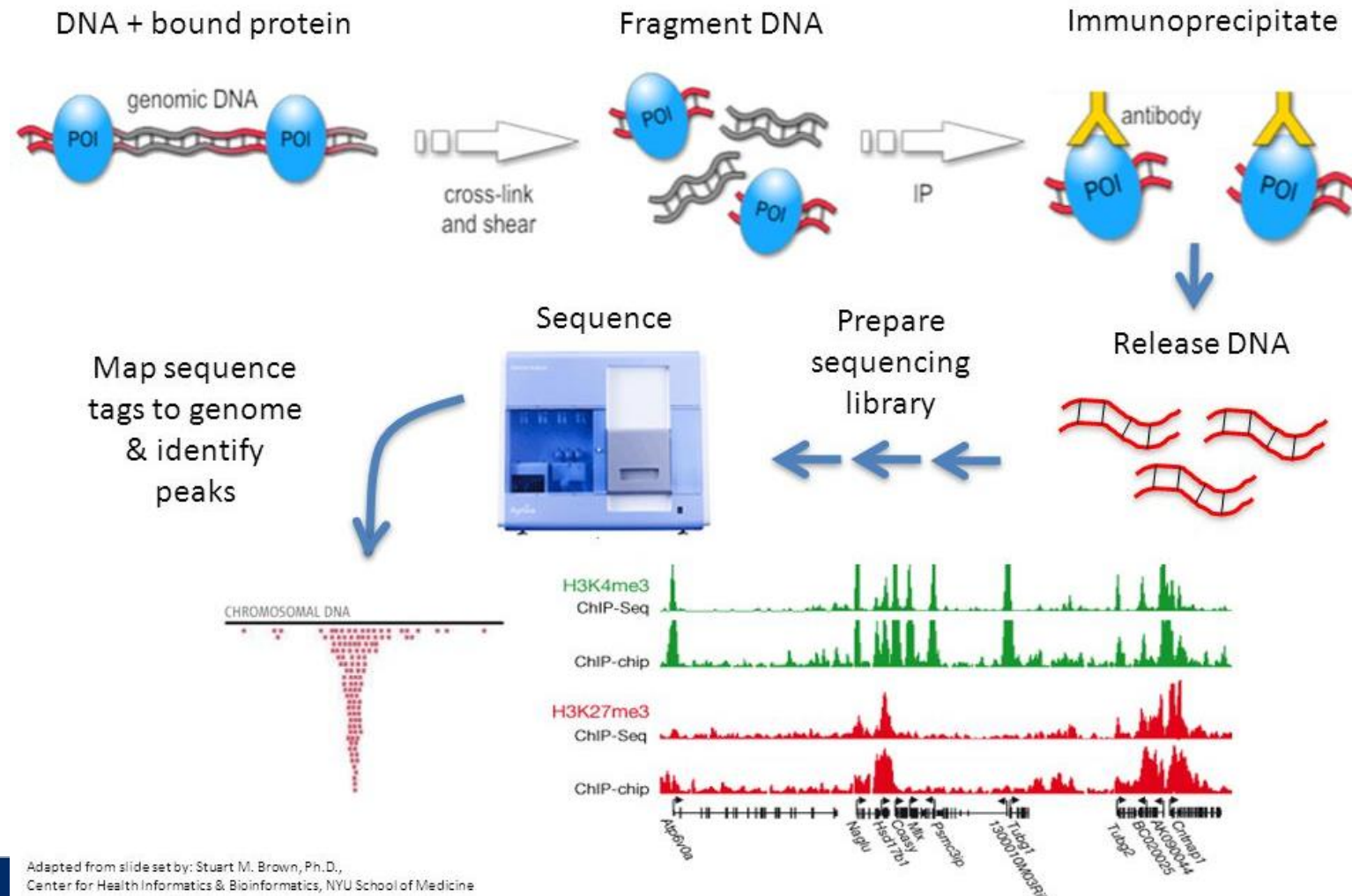
IFN-I & IFN-II induced Functional Overlap



Overlap Marks Core
Antiviral &
Immune Response
Functions

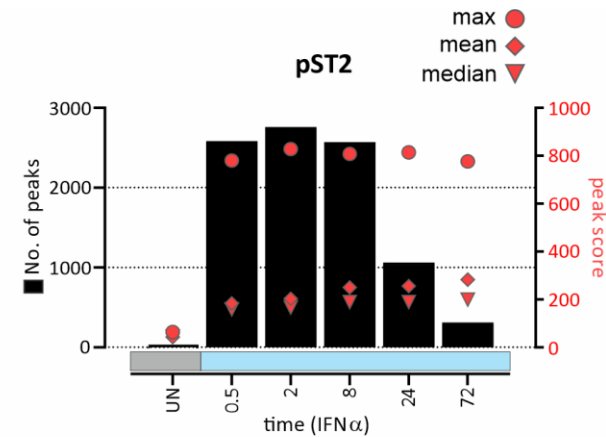
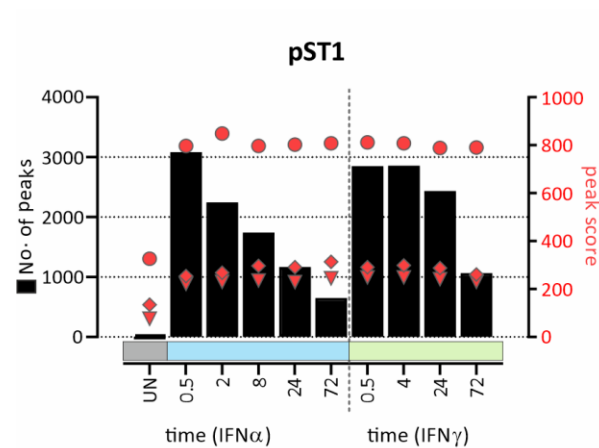
How to analyze chromatin
interactions?

ChIPseq Workflow

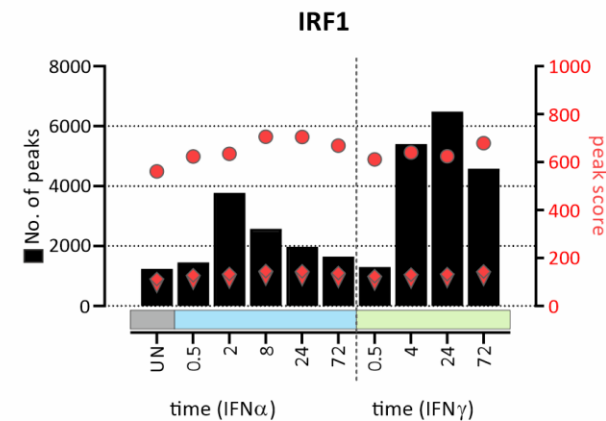
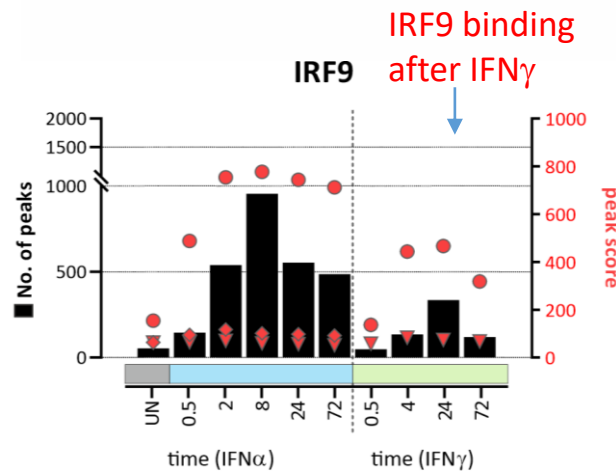


Genome-wide IFN-I & IFN-II induced Chromatin interactions in Time

IFN-induced
Binding

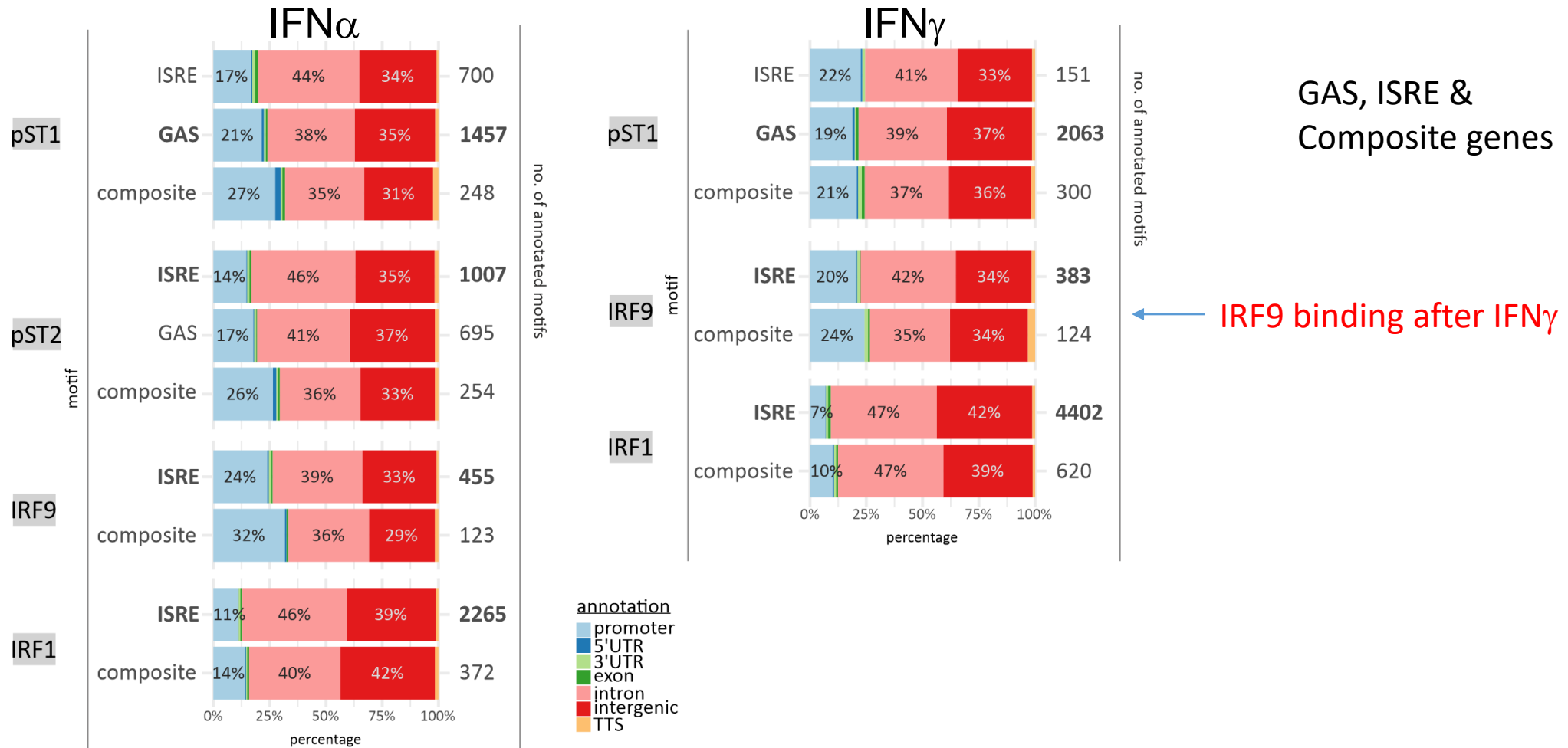


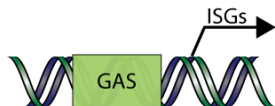
IFN-induced
Binding



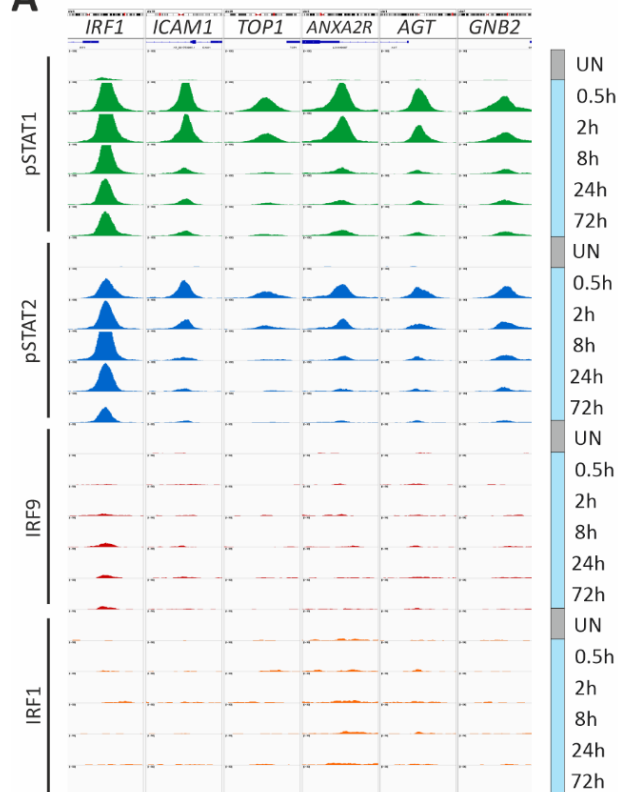
Basal + IFN-induced
Binding

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

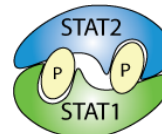




A

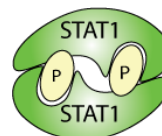


GAS-only

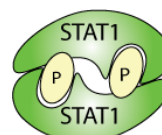
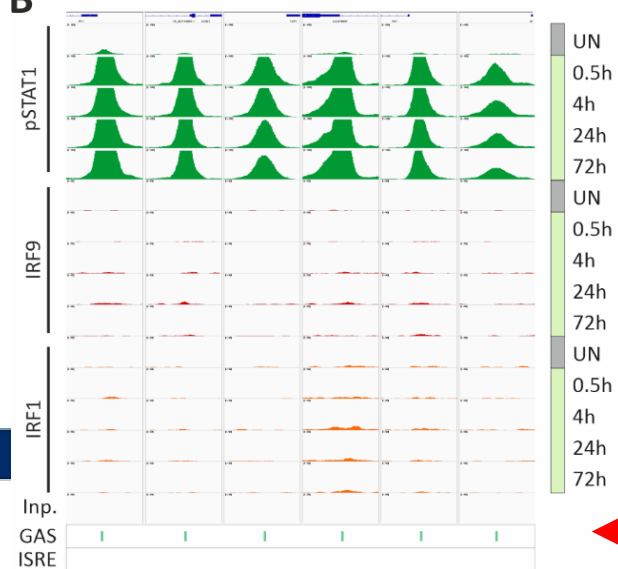


IFN α

EARLY



B



IFN γ

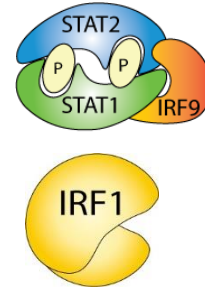
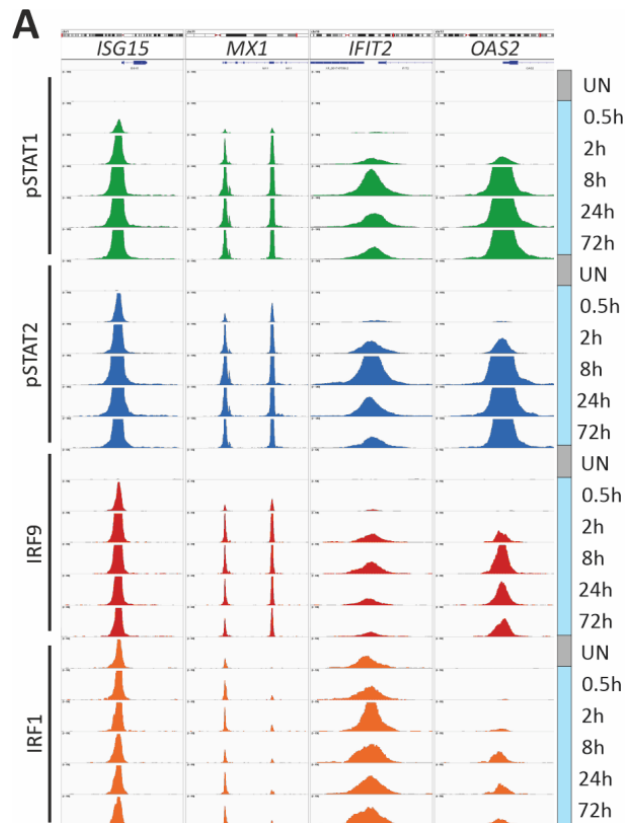
Prolonged



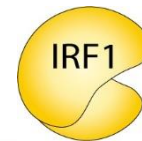
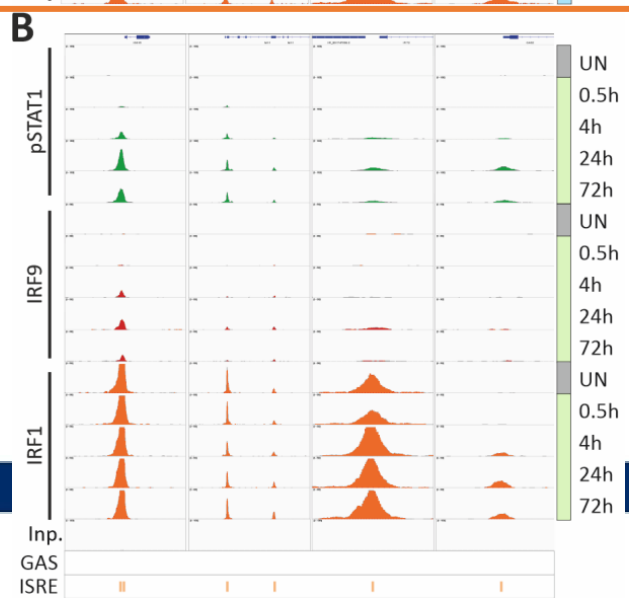
Sekrecka et al. in preparation



ISRE-only



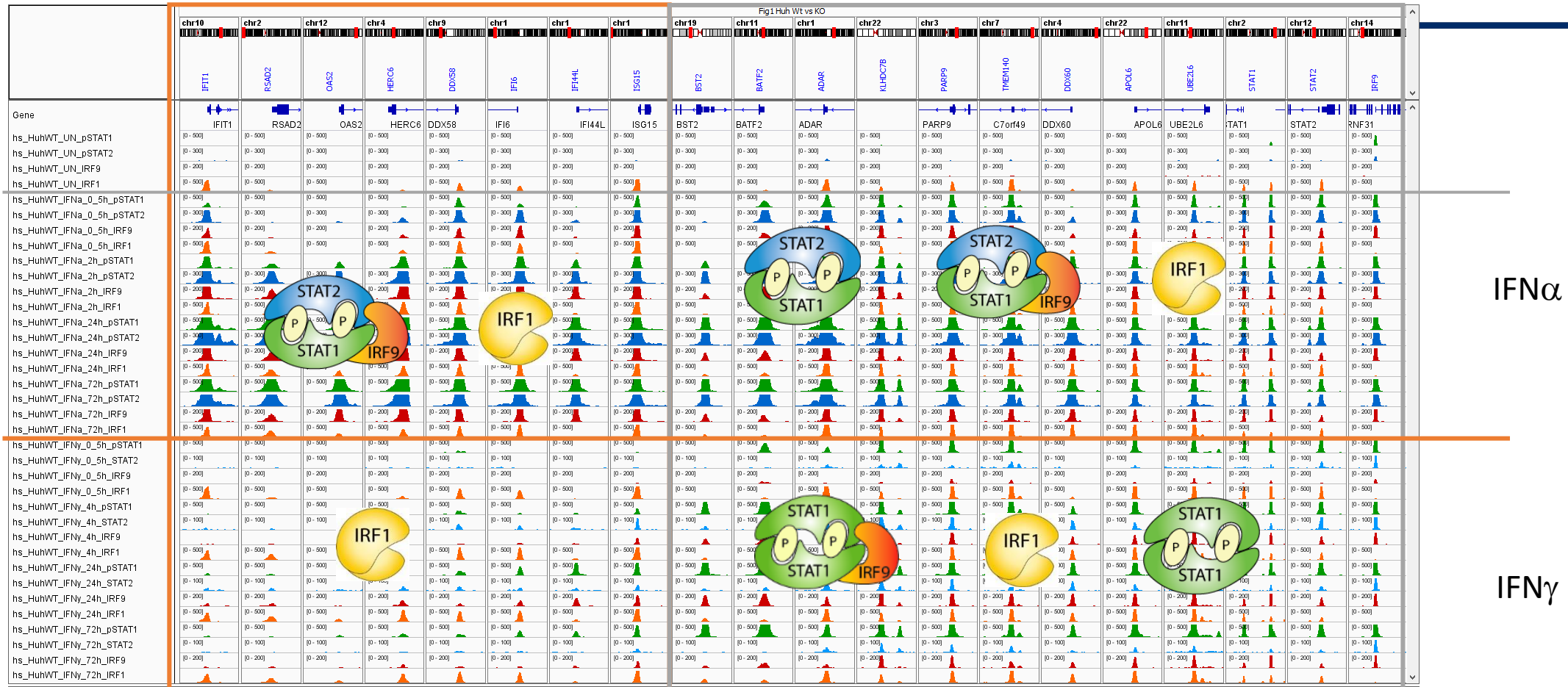
IFN α



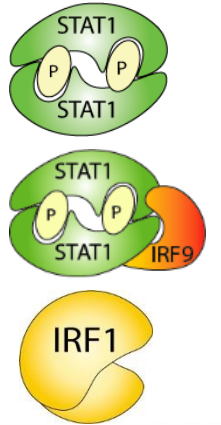
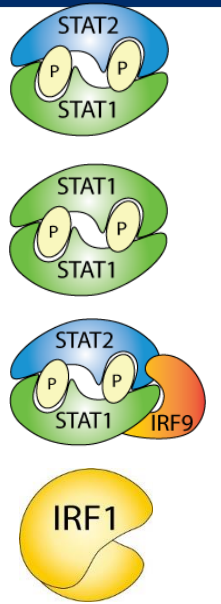
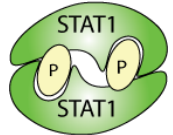
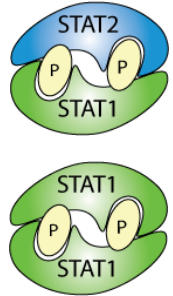
IFN γ



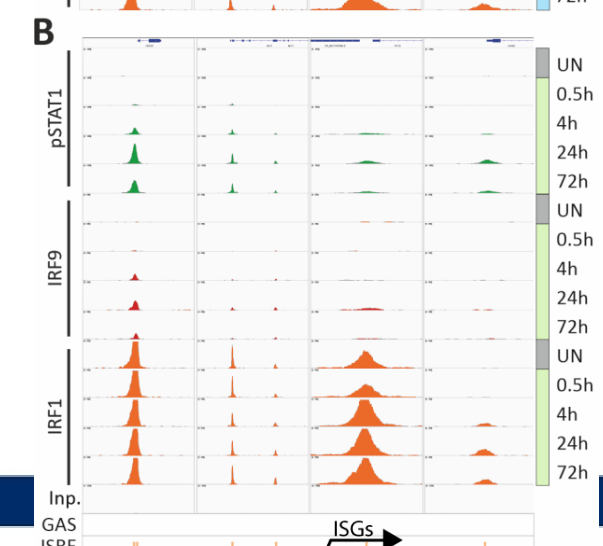
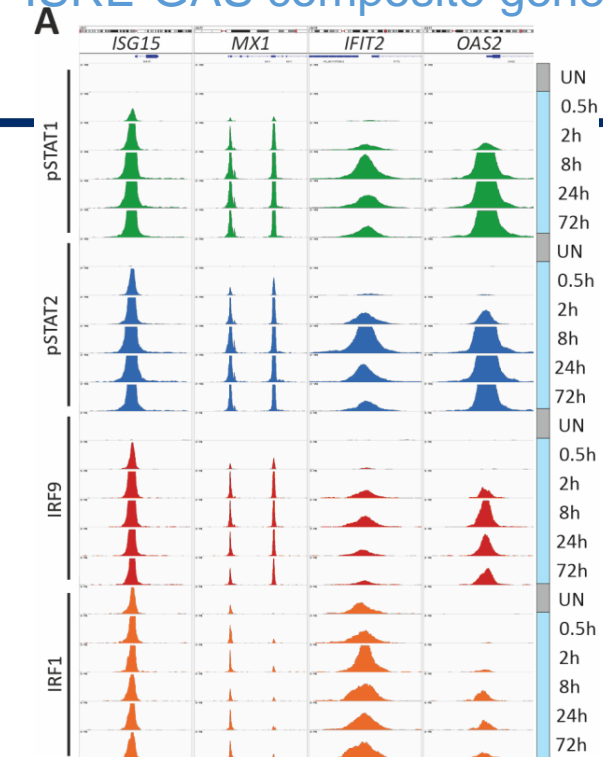
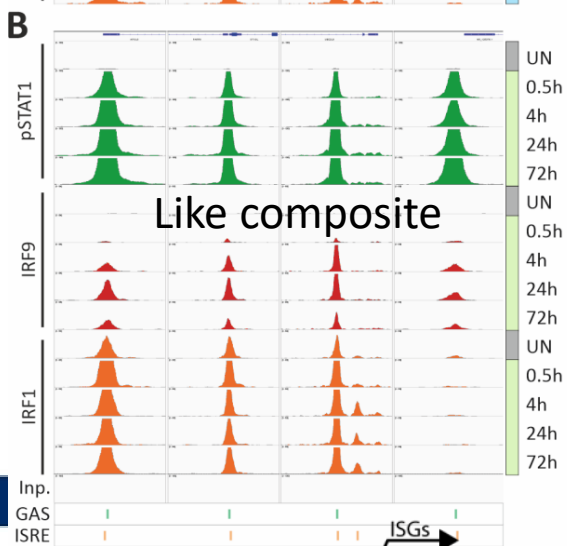
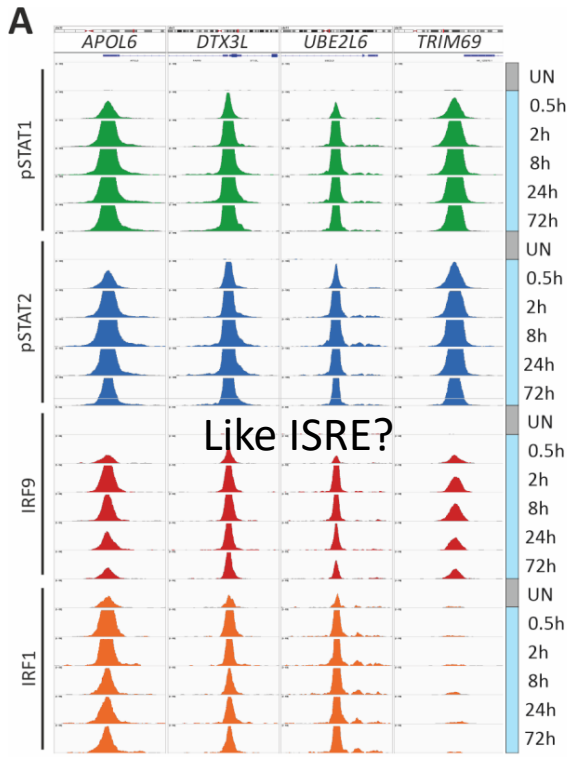
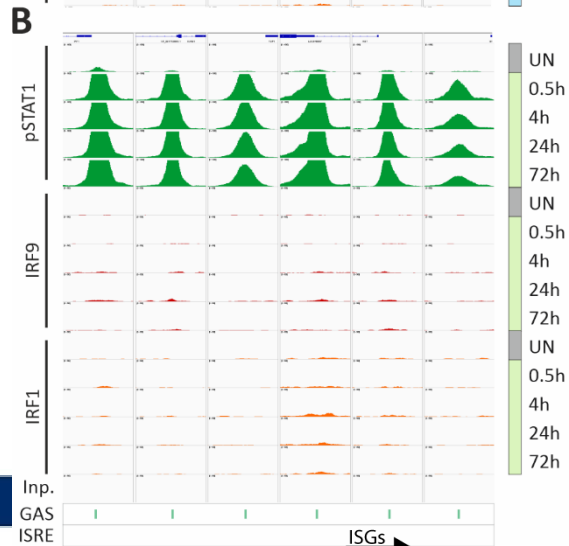
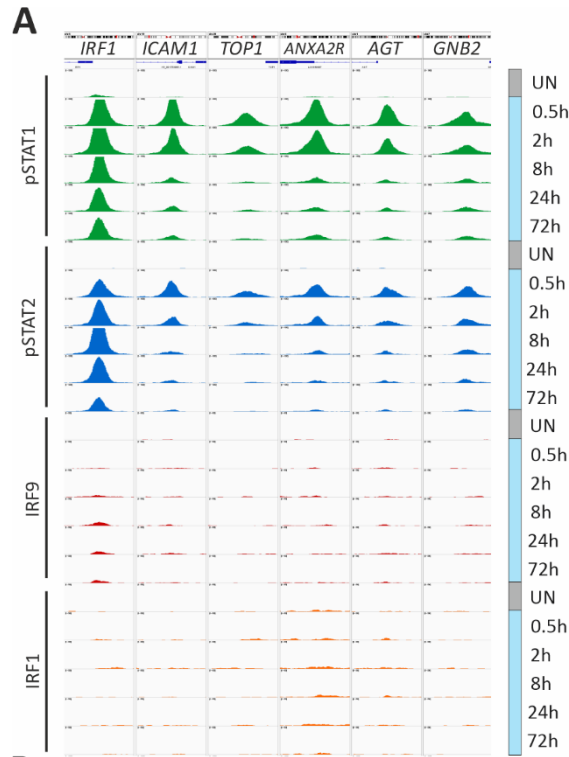
Differential complex binding to ISRE and ISRE-GAS Composite genes



Earlier



ISRE-GAS composite genes show combined binding features

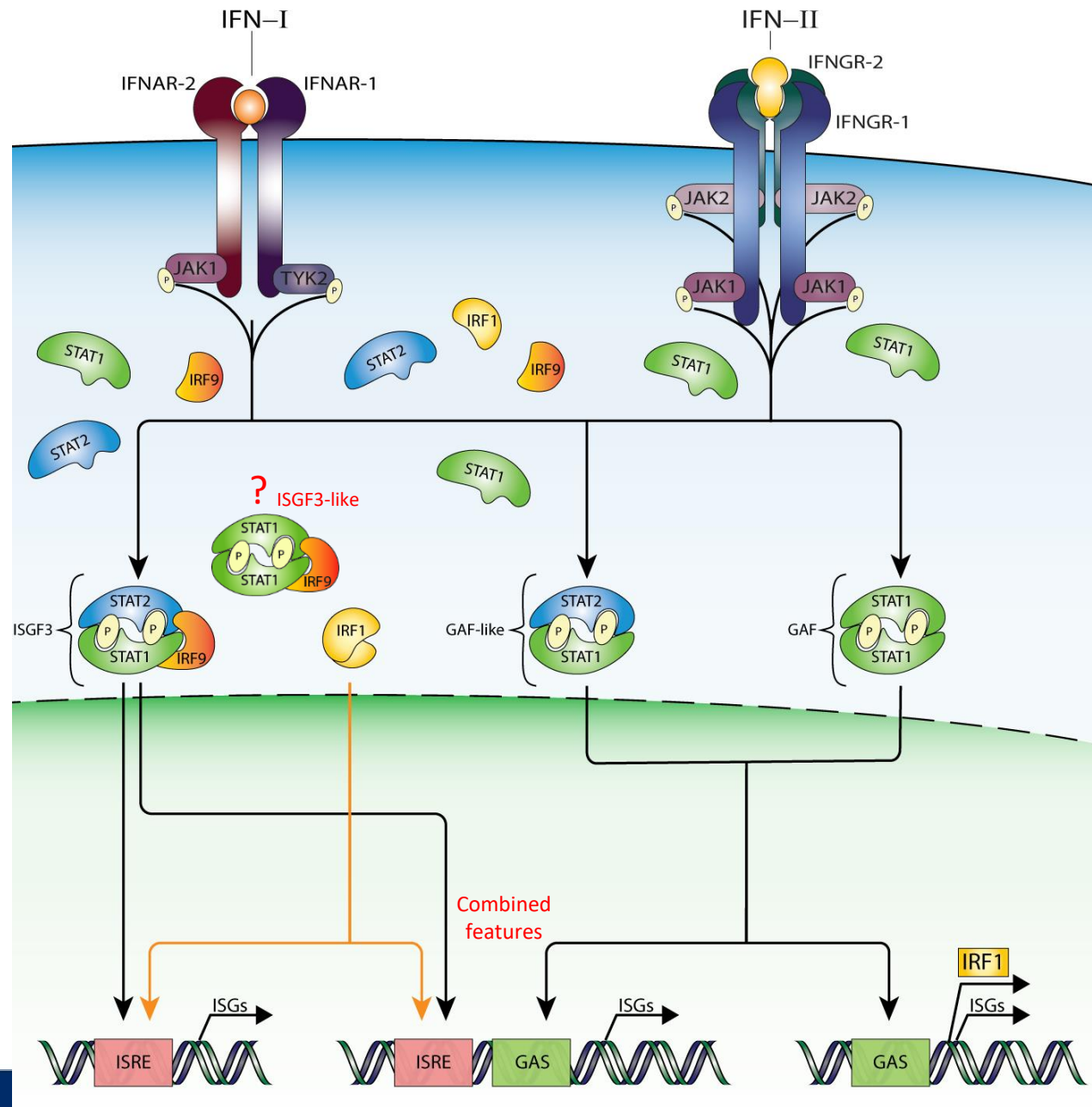


Sekrecka et al. in preparation

ISGF3, ISGF3-like
GAF, GAF-like
and IRF1

ISRE-GAS
Single or
Composite sites

Transcriptional
Overlap

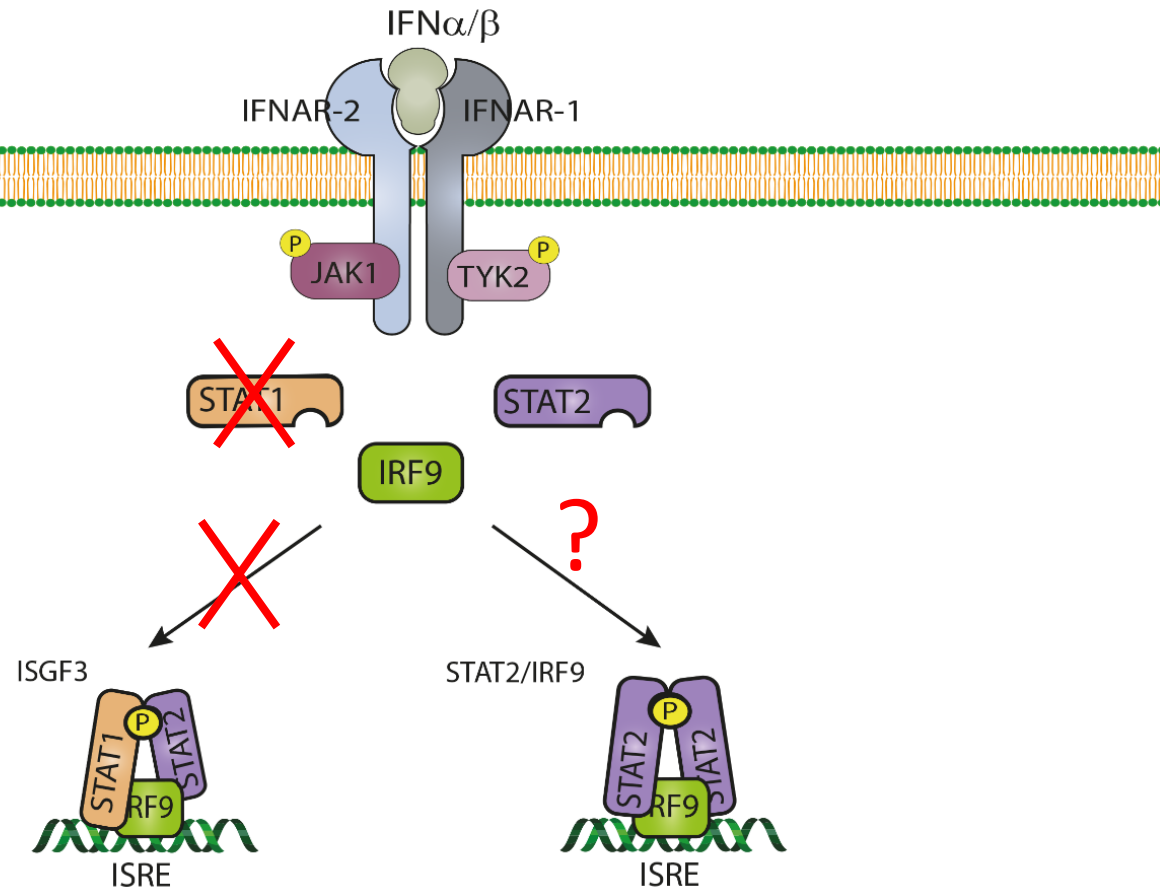


What are the IFN and
Time-dependent
Transcriptional
Regulatory mechanisms of
GAS, ISRE and composite
Genes?

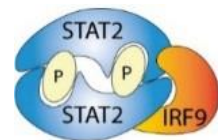
How does that shape
The Antiviral Response?

Alternative IFN-I-signaling in the absence of STAT1

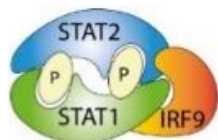
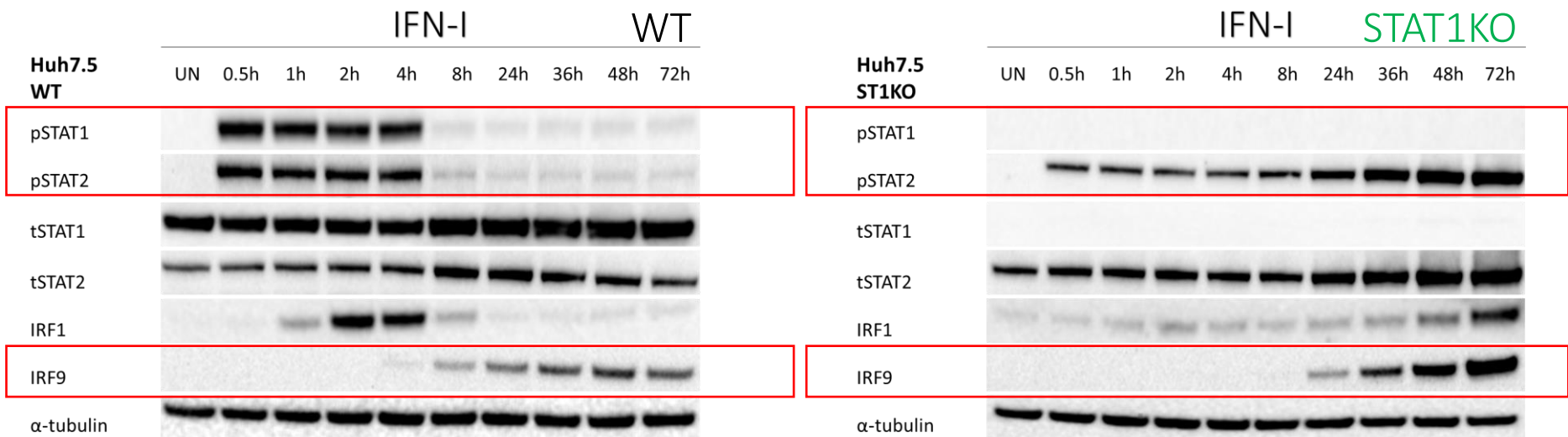
Non-Canonical
IFN-
signaling

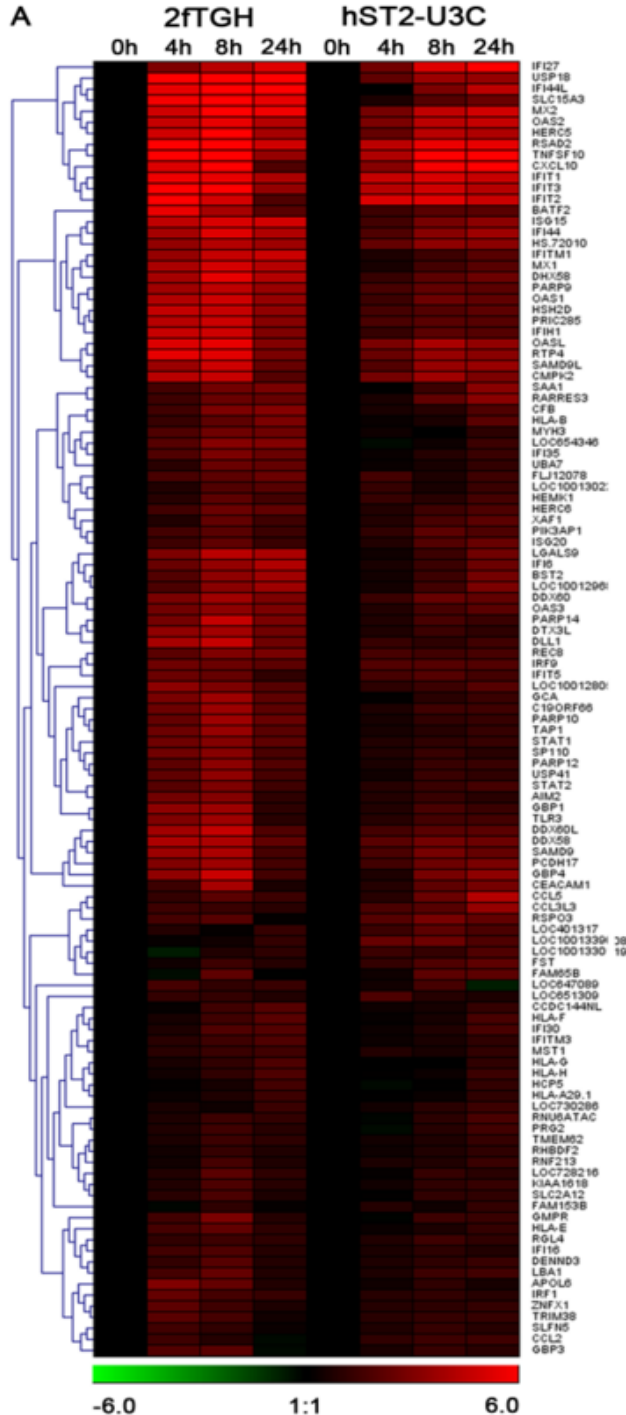


Alternative complexes: IFN-I-signaling in the absence of STAT1



Bluyssen HAR & Levy DE JBC 1997

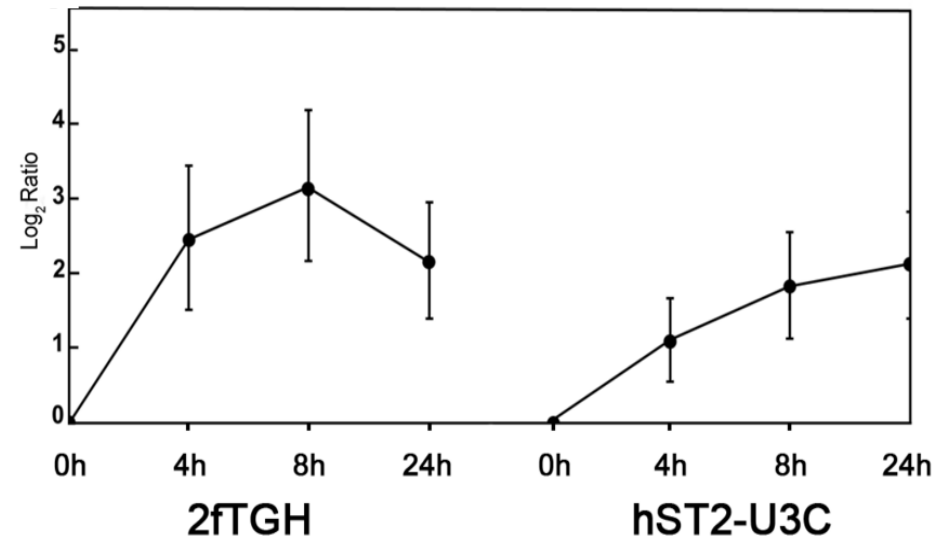




IFN-I Signaling: ISGF3 vs STAT2/IRF9

Genome-wide characterization

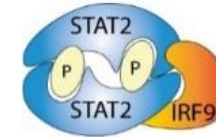
Commonly up-regulated ISGs






EARLY



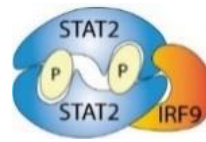
LATE



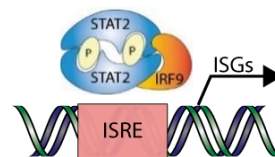
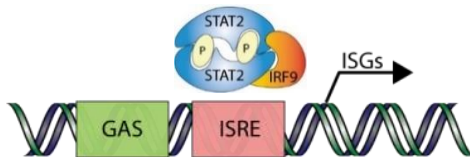
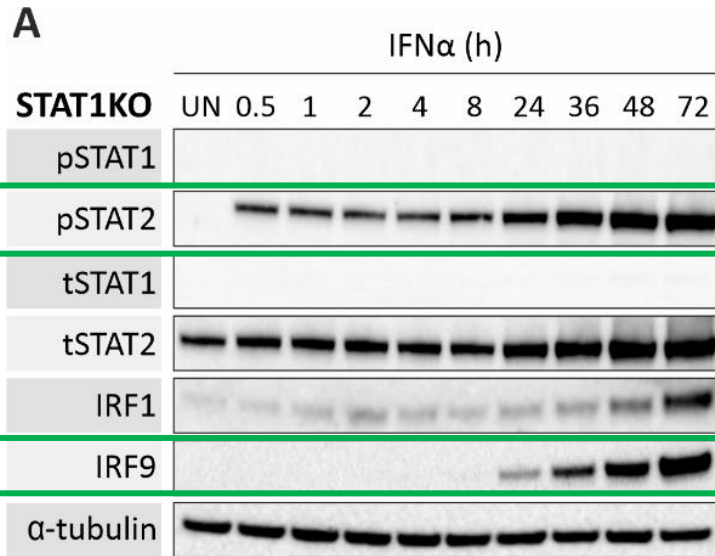
STAT2/IRF9 binds classical ISRE-containing ISGs

ChIP	ISRE-Motif	p-value	%Target	%Background
IRF9 2h		1e-161	38.79%	0.30%
IRF9 24h		1e-240	34.53%	0.34%
STAT2 24h		1e-71	26.89%	0.95%

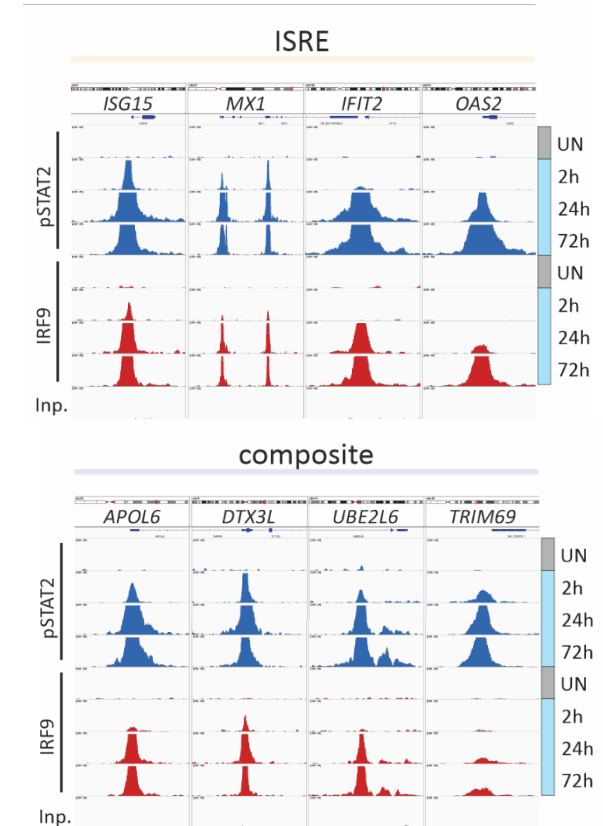




STAT1KO: IFN α Switch to ISRE-only + Prolonged response

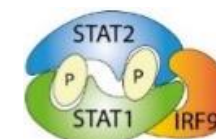
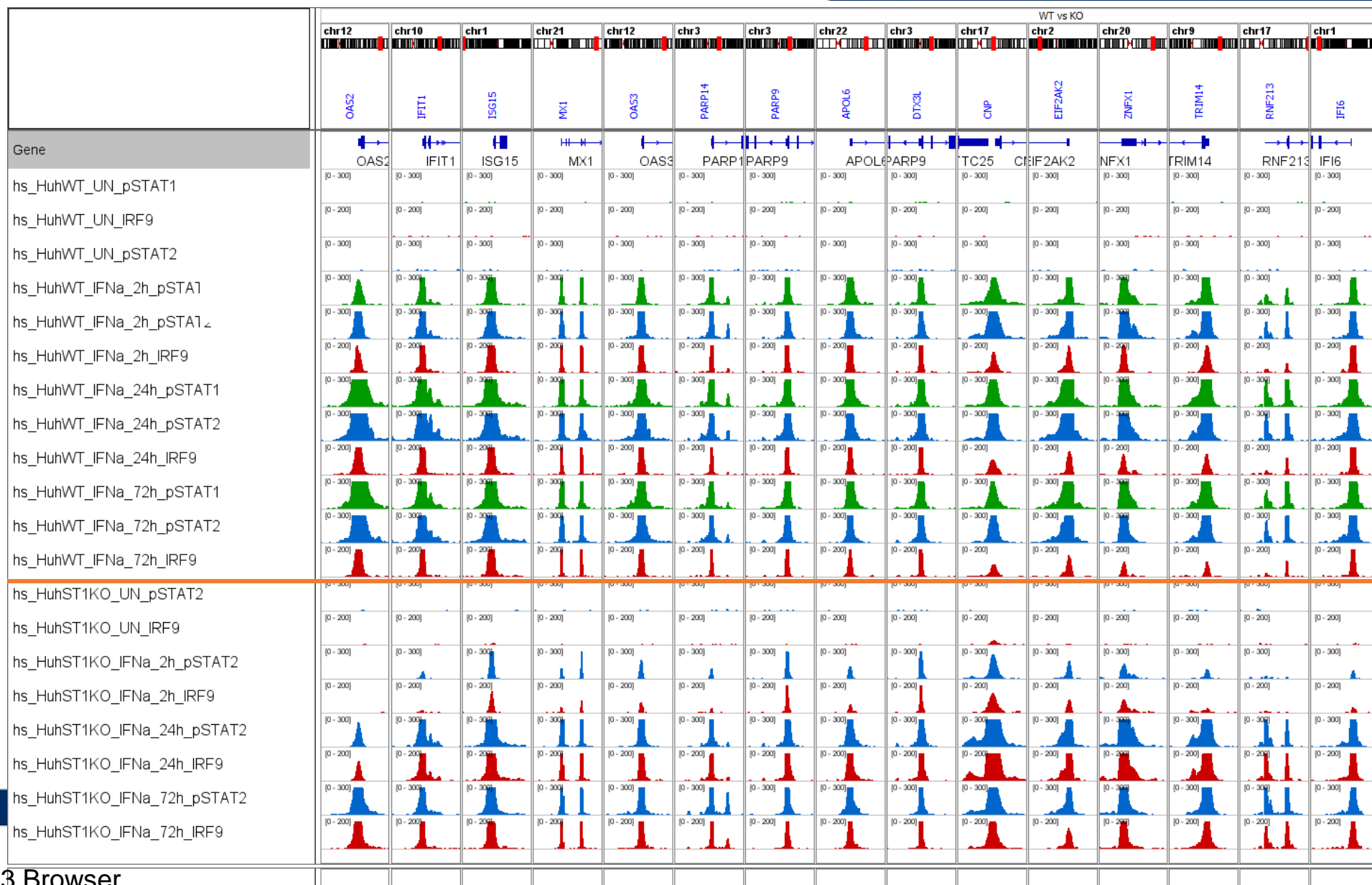


In the absence of STAT1, STAT2/IRF9 takes over the role of ISGF3



Huh7.5-STAT1KO

IFN-I Signaling: ISGF3 vs STAT2/IRF9



ISGF3: EARLY

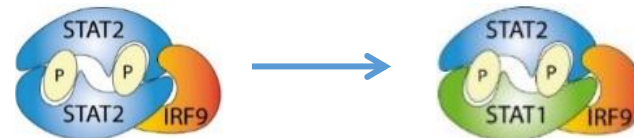
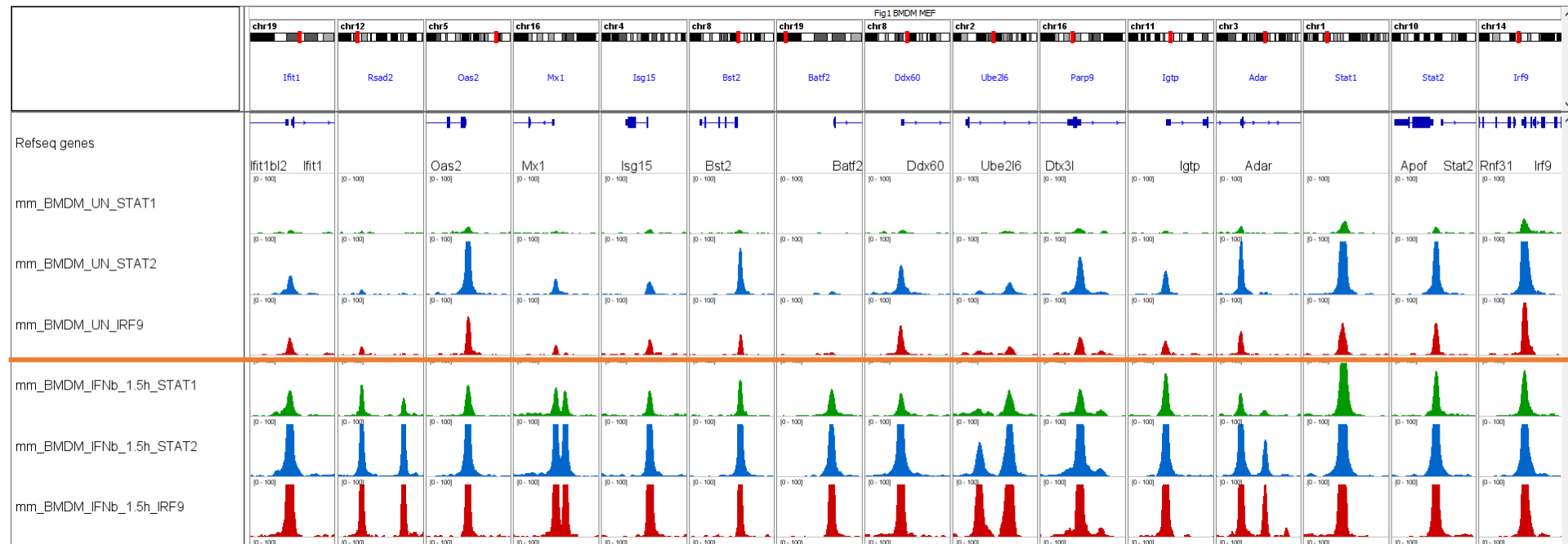


STAT2/IRF9: LATE

Michalska et al.

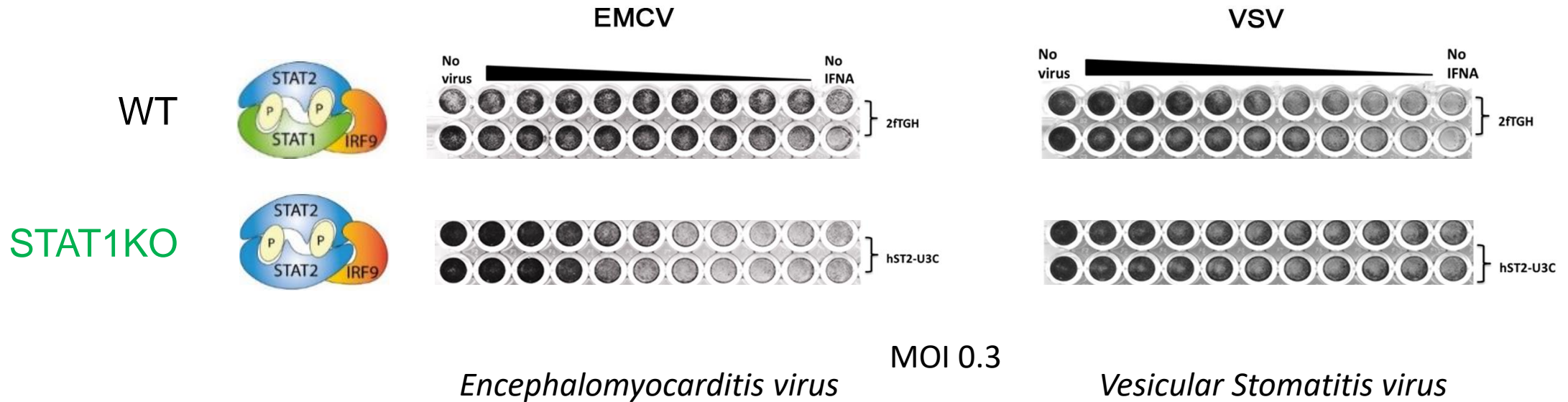
Mouse BMDM

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



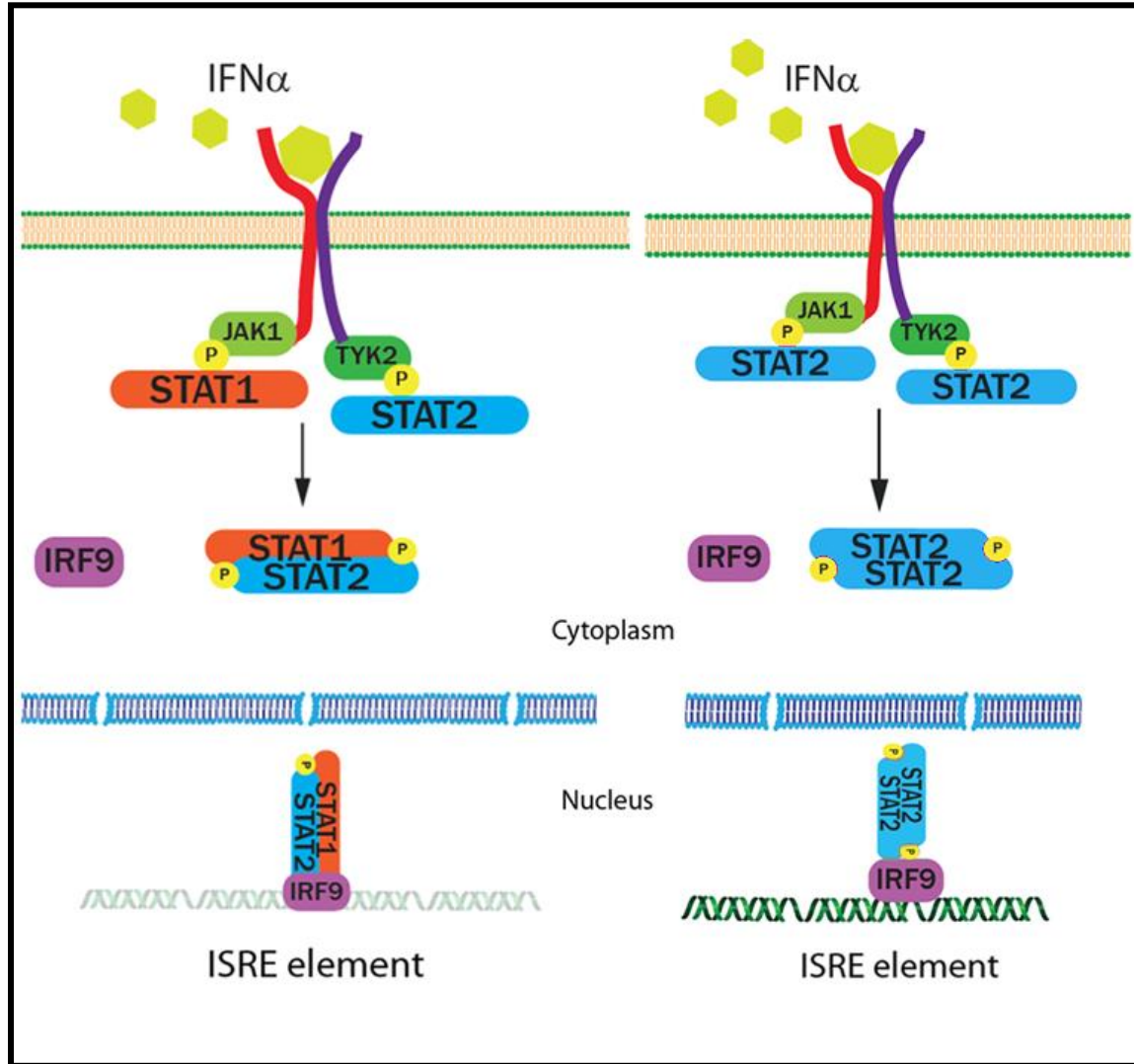
STAT2/IRF9 Reconstitutes IFN-I-mediated Anti-viral responses

Biological Function!



STAT2/IRF9 Reconstitutes IFN-I-mediated responses

Canonical
ISGF3:
TRANSIENT



Non-canonical
STAT2/IRF9:
PROLONGED

Viral Immune
Evasion



Alternative anti-viral
strategies

Evolutionary
back-up
response!

TEAM

UAM, IMBB

Lab of HMG & HTT

Prof J. Wesoly

Dr. Natalia Derebecka

Dr. Katarzyna Kluzek

Dr. Michal Sekrecki

**Dr. Mahdi Eskandarian
Boroujeni**

Hanna Nowicka

Agata Sekrecka

Martyna Plens Gałąska

Aleksandra Antonczyk

Sanaz Hassani

Natalia Lopacinska

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