From virus infection to cancer: The interferon paradox

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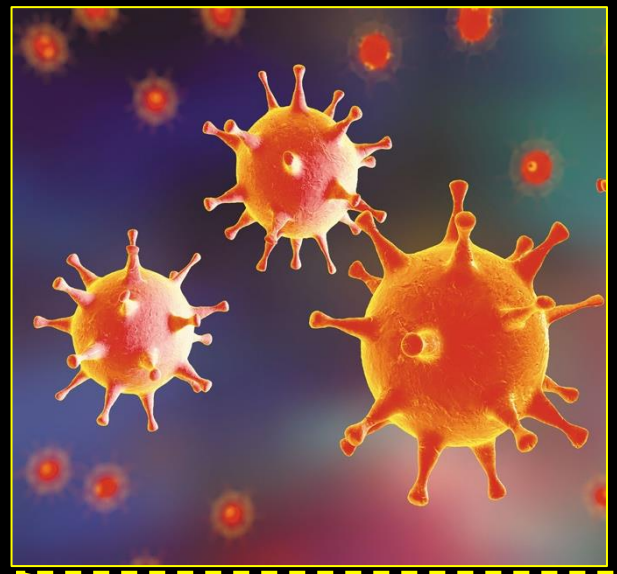
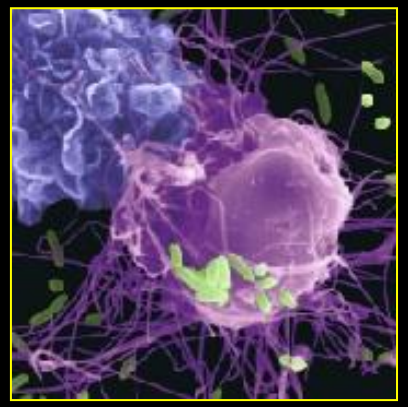
Our Research Focus: Immunity to chronic disease

Chronic virus



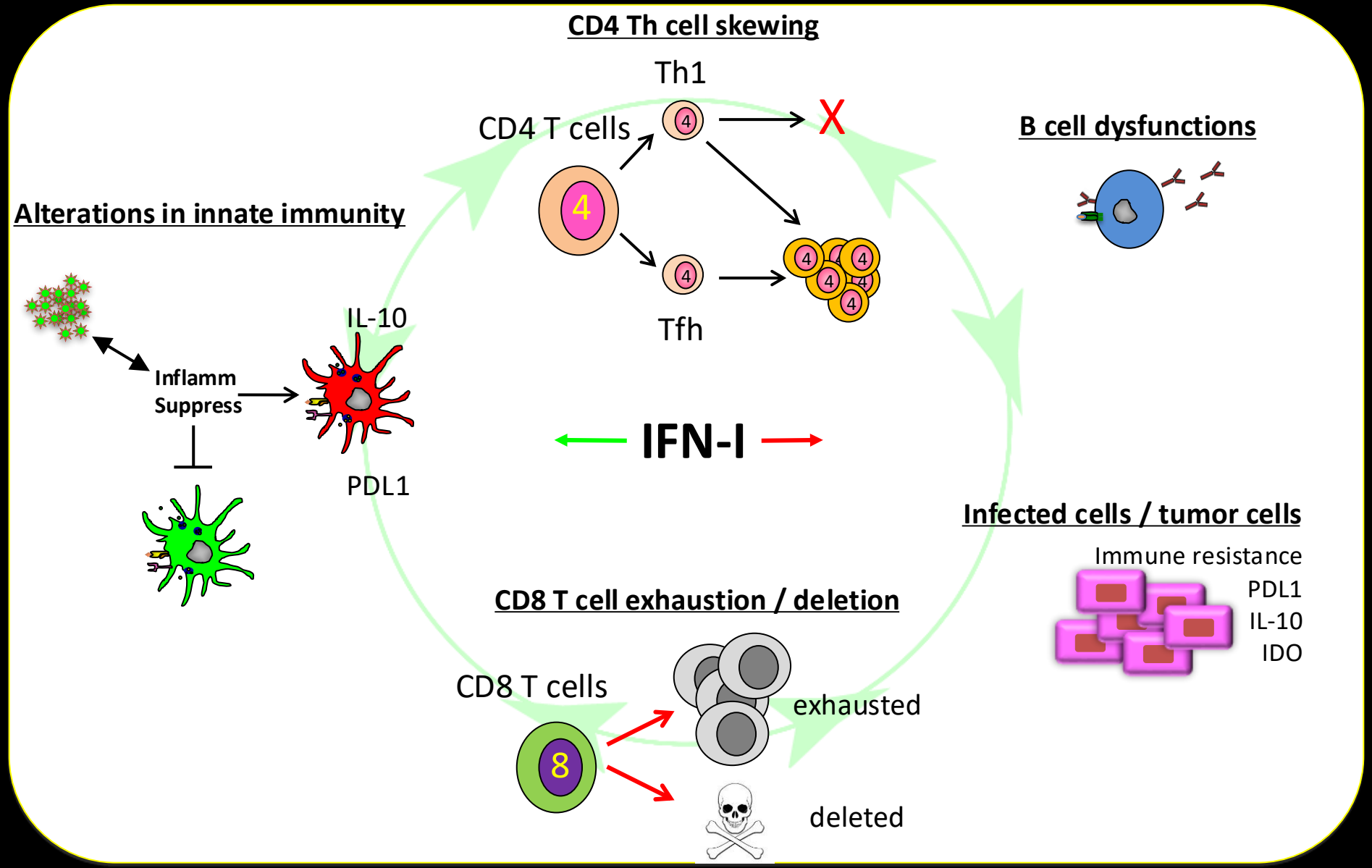
Cancer



Host Immunity

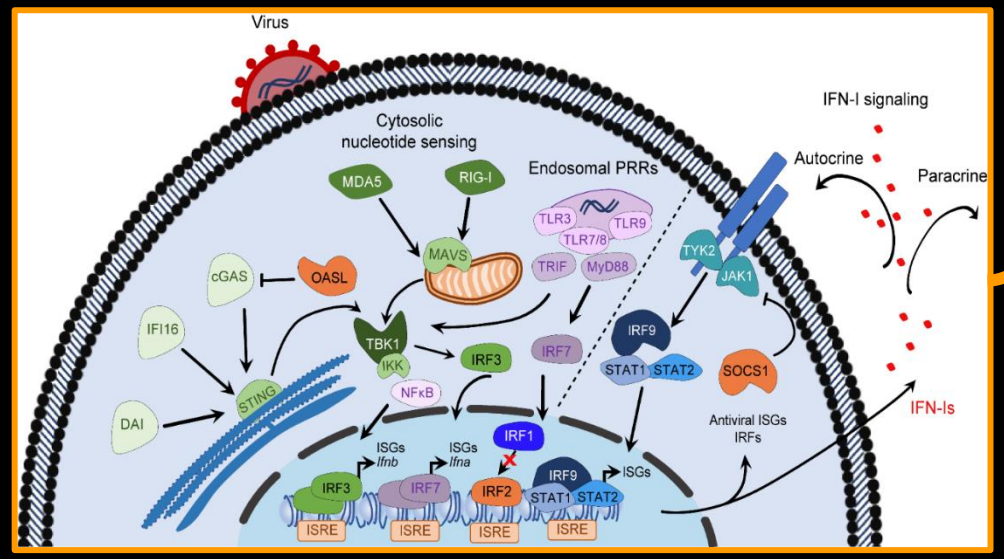
Shared and divergent mechanism of inflammation, immunosuppression, immune dysfunction and opportunities for immunotherapy

Convergence of multiple inflammatory and immunosuppressive mechanisms inhibit immunity during viral persistence



Type I interferons (IFN-I) induce a series of signaling molecules and pathways to induce 100s of interferon stimulated genes (ISGs)

Induction of IFN-Is



Lukhele, Boukhaled, Brooks. Sem Imm 2019

Type I interferons (IFNα/β)

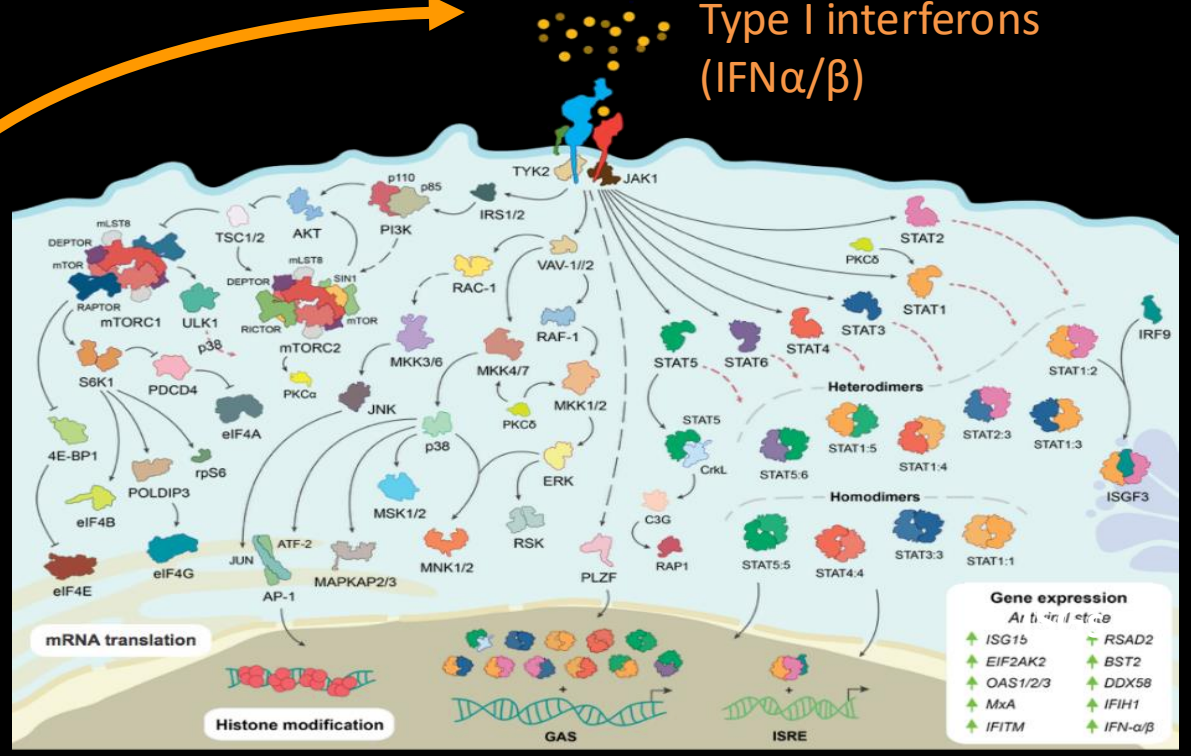


Image provided by Eleanor Fish

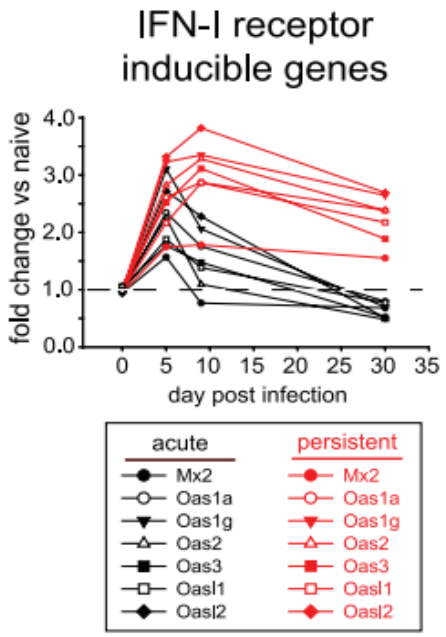
Antiviral / Pro-inflammatory

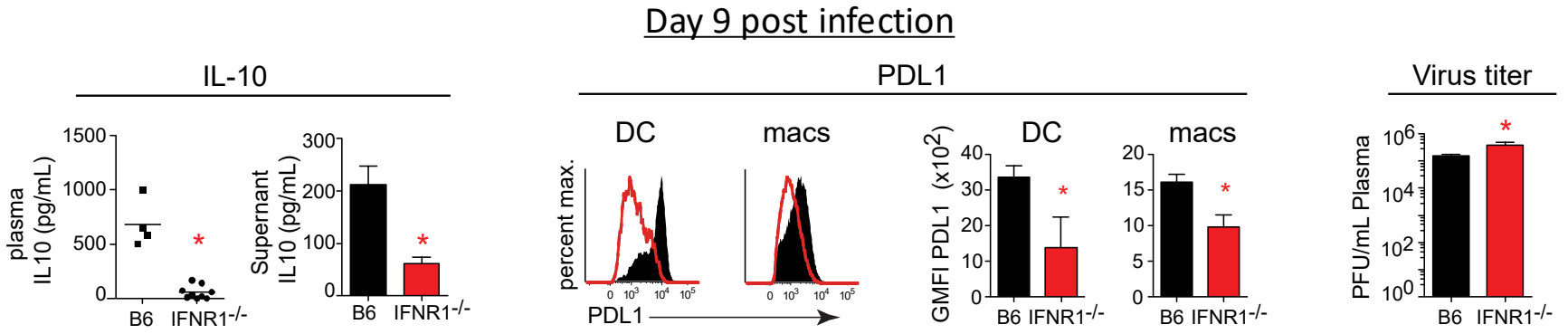
Anti-inflammatory

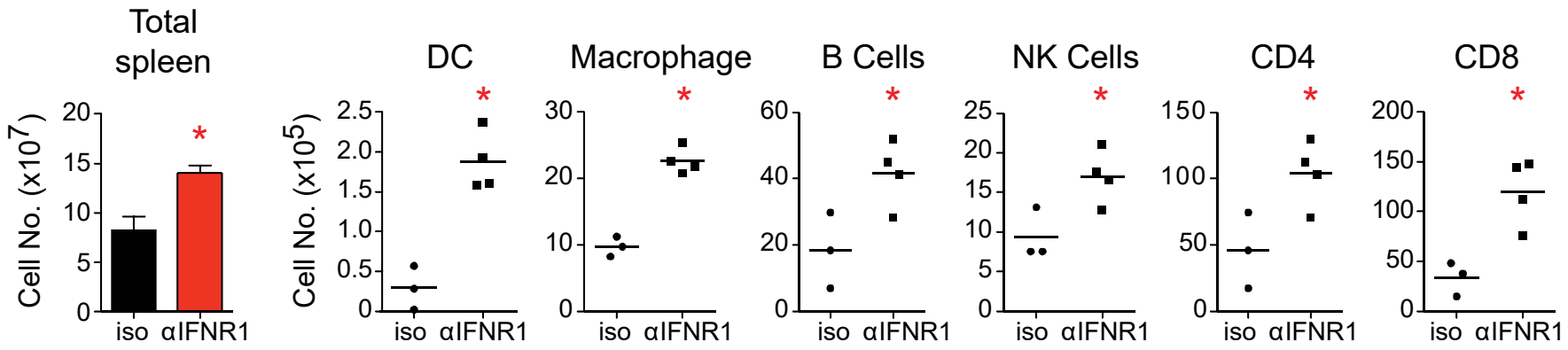
How did we come to be interested in interferons?

It started with a virus controlled acute infection to identify factors that promote immunosuppression

IFN-I signaling was critical for viral control and the ensuing lymphocytic choriomeningitis (LCMV) environment







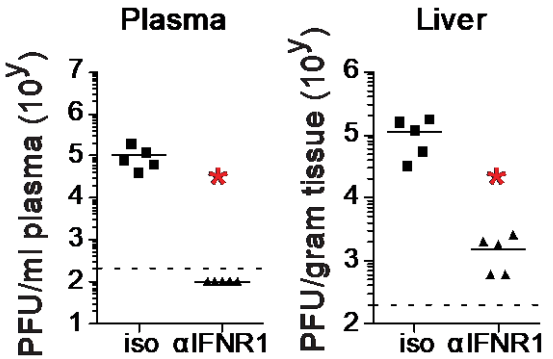
Wilson et al., *Cell Host and Microbe* 2012
Wilson et al., *Science* 2013

Transient blockade of IFN-I signaling enhances control of chronic LCMV infection

Chronic LCMV

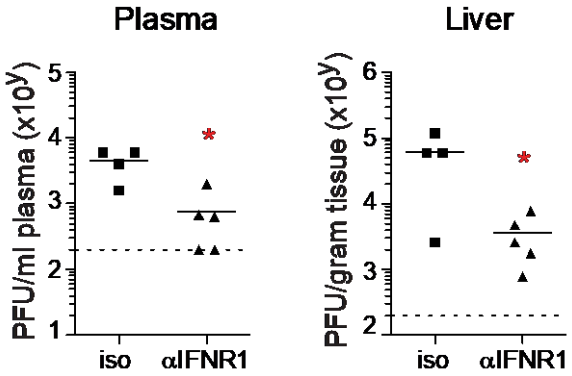
Early anti-IFNR1 block
(*days -1 to 8 post infection*)

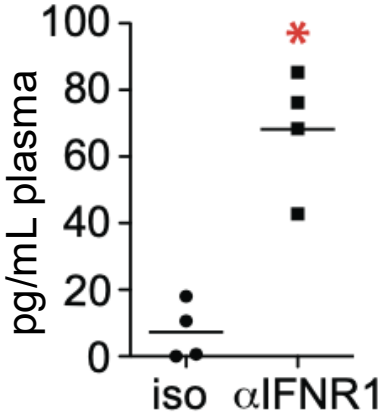
Day 30



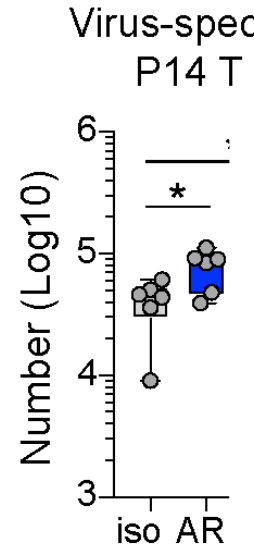
Late anti-IFNR1 block
(*days 24-29 post infection*)

Day 46



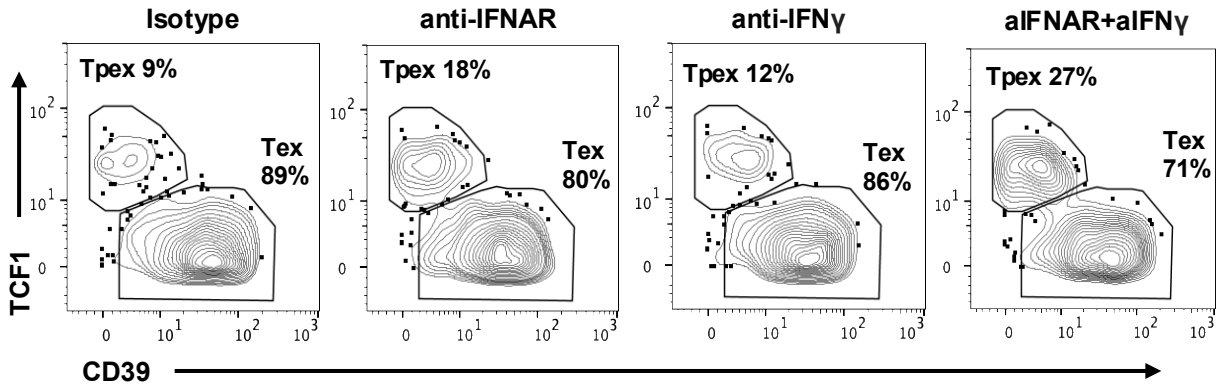


Day 35



Wilson et al., *Science* 2013

Specific increase in amount of T progenitor exhausted (Tpex) subset that replenishes the effector cells in chronic infection (and cancer) and is the subset that responds to anti-PD1 immunotherapy



Liu et al., *in submission*

Conclusions- *virus side*

- IFN-Is regulate the induction of multiple suppressive factors that prevent and long-term limit control of chronic infection
    - *IFN-Is translate information about virus replication to modulate the ensuing immune response*
    - *IFN-Is diminish expression of the pro-inflammatory cytokine IFNg*
- IFN-Is restrict Tpex proliferation and differentiation by inducing IFNg expression that upregulates PDL1 expression (Elsaesser et al., *in submission)*.
- Double IFN-I and IFNg blockade overcomes the dual safe-guarded suppression to enable Tpex expansion, potentially explaining (at least in part) why IFN-I blockade enhances virus control

Currently exploring…

- Other factors that contribute to the IFN induced immune modulation
- The distinct contributions of IFN alpha vs IFN beta to provide antiviral activity, regulate immunosuppressive factors and T cell differentiation in chronic infection.

Type I IFNs (IFN-Is) are central regulators of the hallmarks of cancer

Type I interferons (IFN-Is; IFNα and IFNβ) are important at all stages of cancer development and disease progression (e.g., promoting APC maturation, effector cell differentiation)

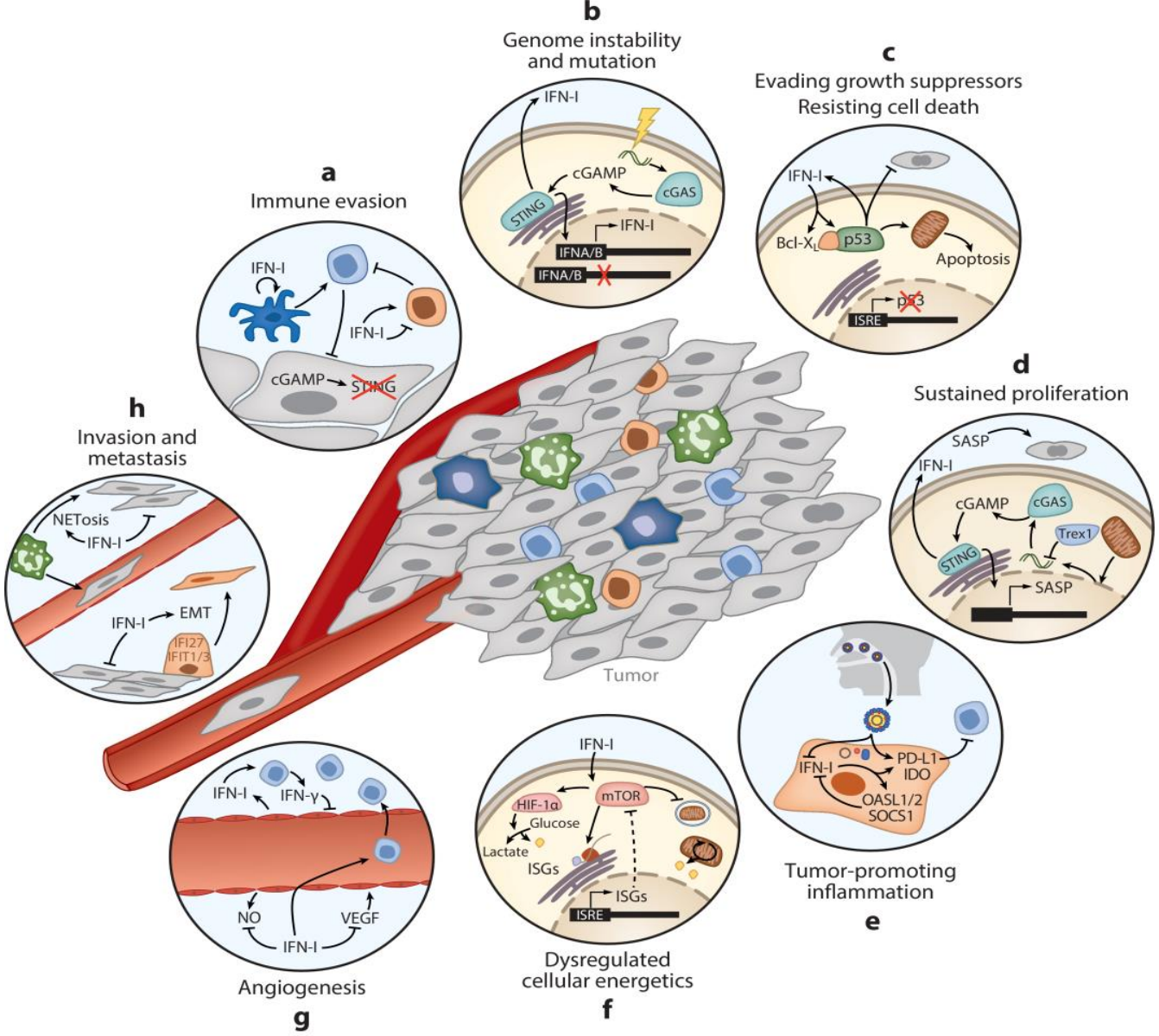
…*however*, IFNs also induce suppressive factors that inhibit anti-tumor immunity (e.g., PDL1, IL10, IDO)

IFN-Is are critical for the beneficial response to cancer therapies, including immune- and radiation- therapy

But also drive therapy resistance limiting these therapies

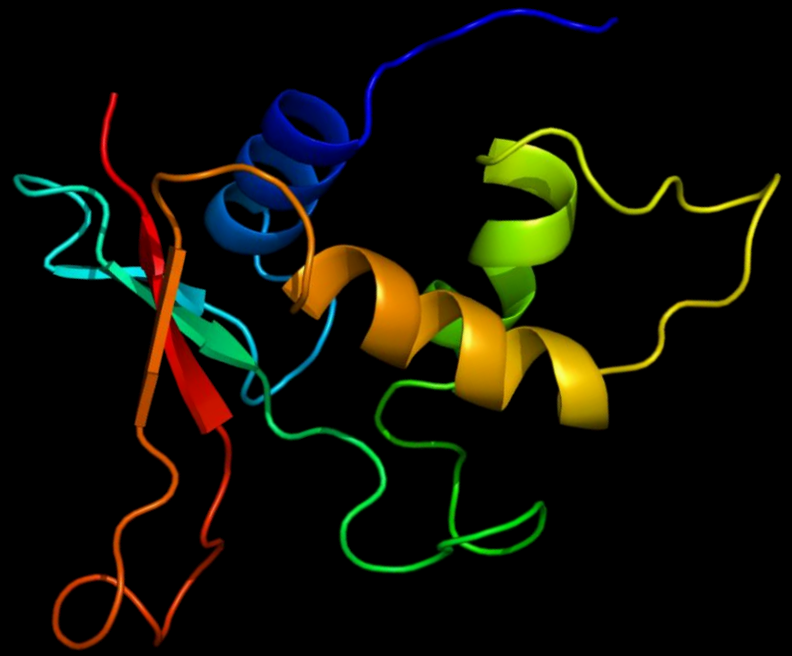
Recent publications show that incorporation of a JAK inhibitor increased the responsiveness to anti-PD1 therapy in NSCLC and Hodgkin lymphoma (Zak et al. and Mathew et al. *Science* 2024).
- indicates ability to modulate IFN signaling to enhance ICB in some patients

What determines the opposing outcomes of type I IFN signaling and can they be uncoupled?



Boukhaled, Harding and Brooks, *Annual Reviews in Pathology* (2021)

Interferon Regulatory Factor 2 (IRF2) is a transcription factor that inhibits proinflammatory functions



IRF2:

- Constitutively expressed, and upregulated by IFNs
- Most notably, IRF2 antagonizes IRF1 to suppress its gene induction
- Interacts and antagonizes other pro-inflammatory factors (IRF1, IRF8, STAT1, NF-kB) to prevent induction of their target genes
- While the transcriptional role of IRF2 is largely repressive, in certain contexts IRF2 activates gene transcription, such as components of MHC I pathway

Cancer cell-intrinsic IRF2 expression:

- High IRF2 expression by tumor cells often correlates with progression of human cancers by repressing cancer cell-intrinsic IFN signaling
- Conversely, IRF2 deletion in tumor cells increases their growth, including by decreasing MHC I expression

But very little known about how IRF2 regulates the immune response

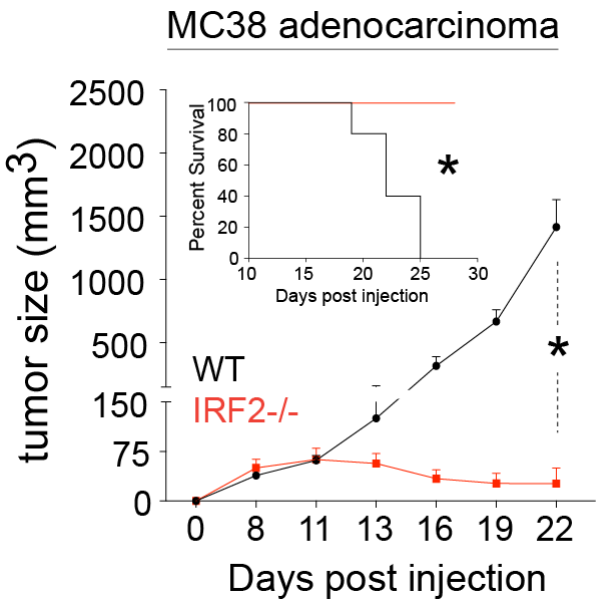
IRF2 deletion enables control of diverse tumor types

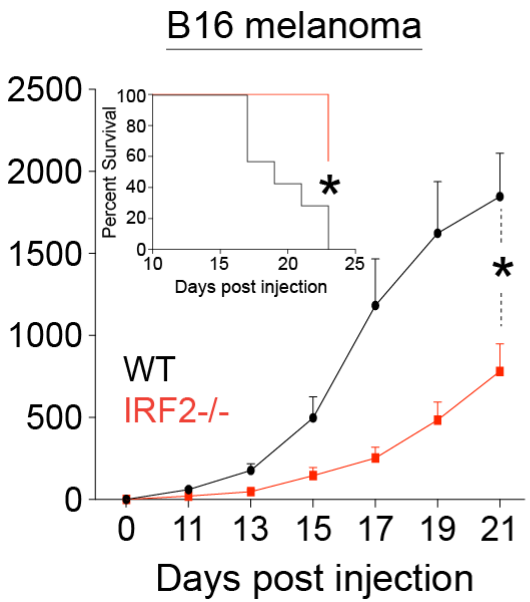
Wild Type
-or-
Irf2 knockout mice

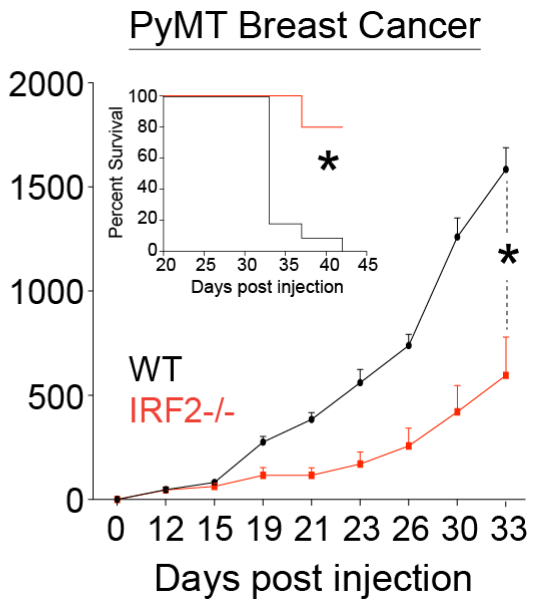
Tumor cells
(*Irf2* sufficient)

Days

Tumor growth
immune analysis





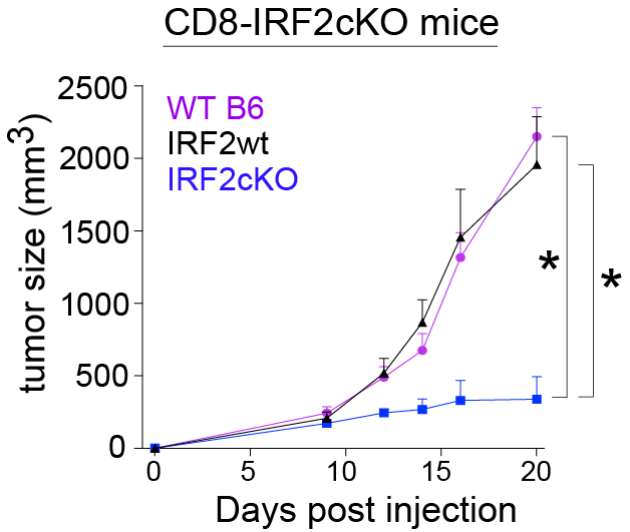


What cells mediate this control?

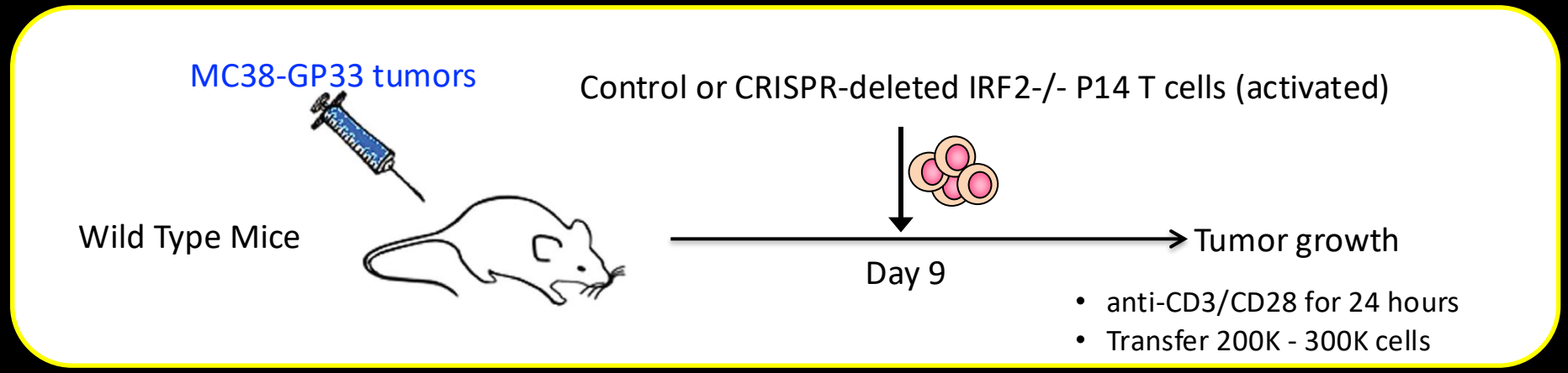
Lukhele et al., *Immunity* 2022

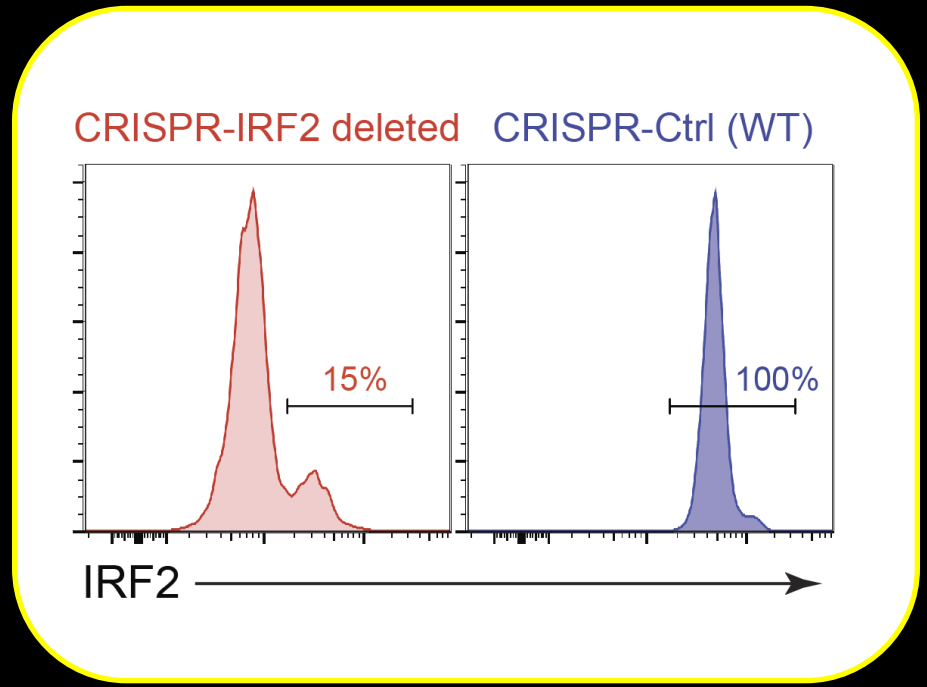
IRF2-deficient CD8 T cells continually control tumor growth

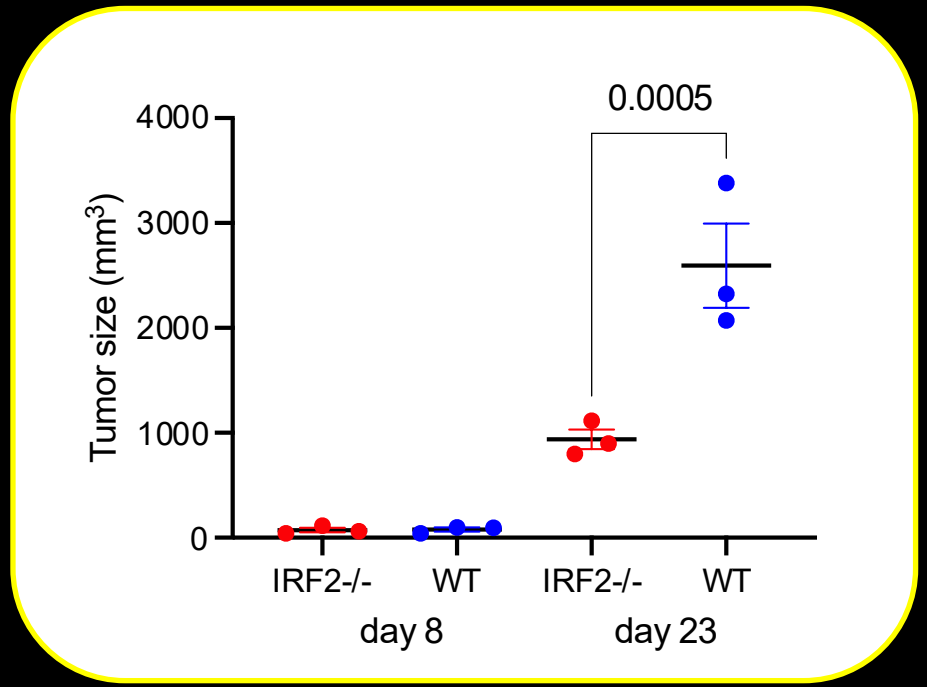
MC38 tumors



Adoptive transfer of IRF2-deficient tumor-specific CD8 T cells delays growth of established tumors

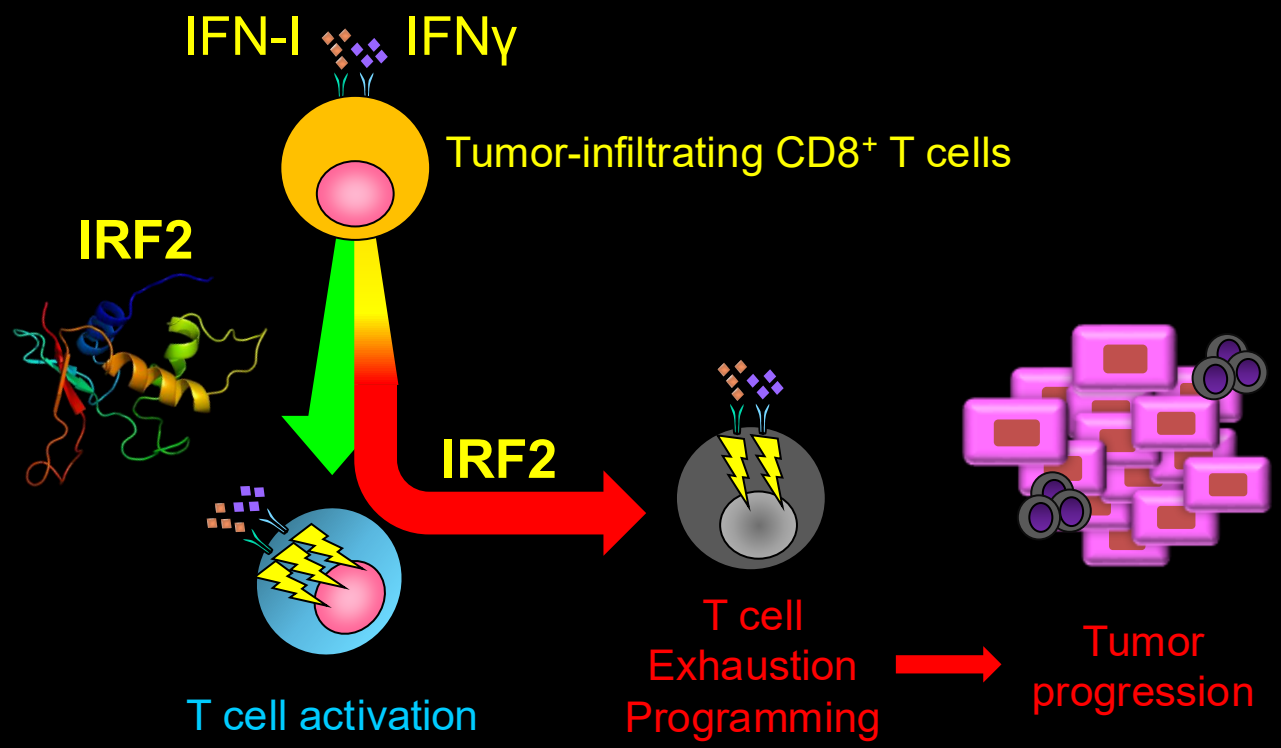






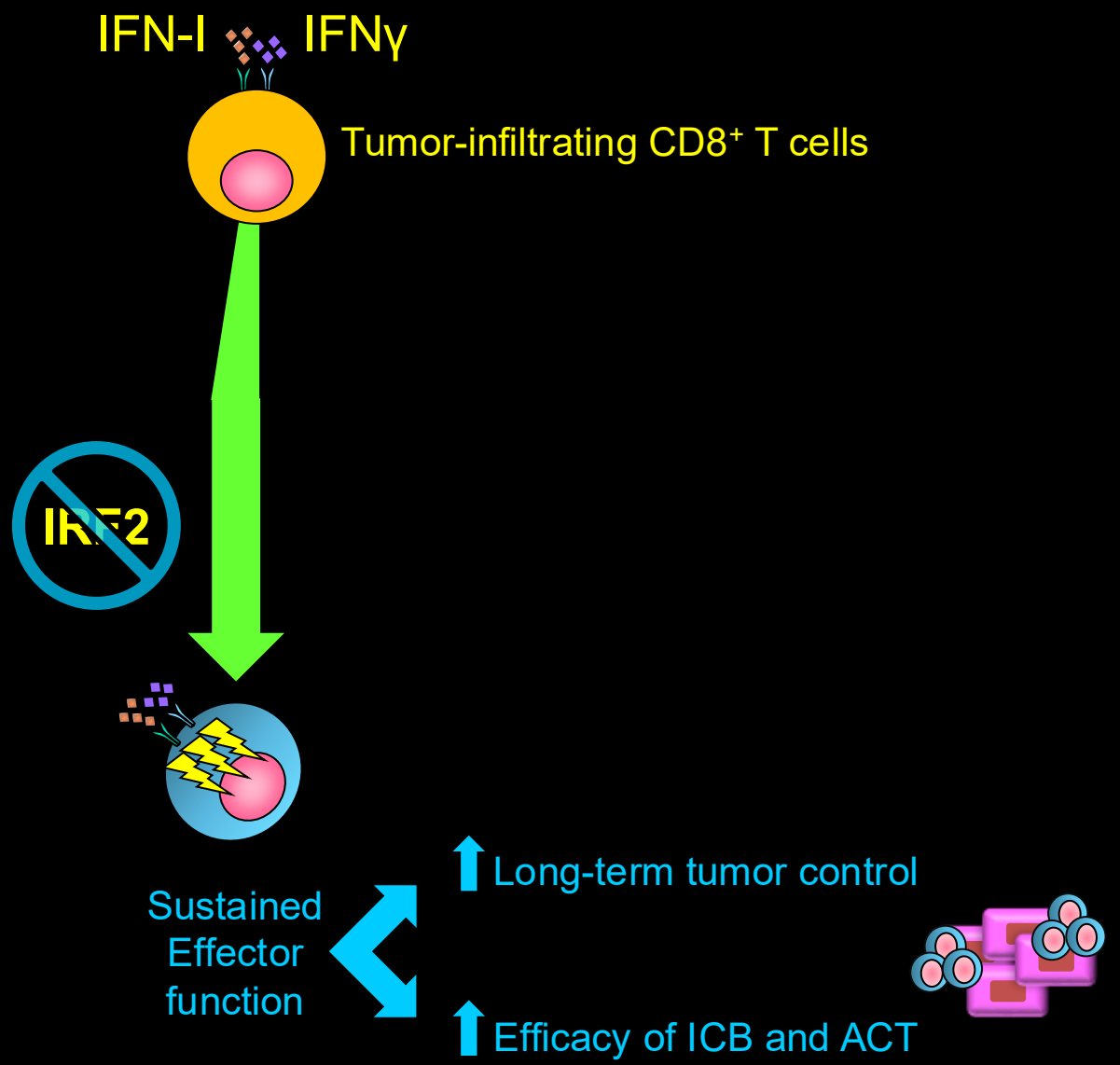
Currently onging: CRISPR deletion of IRF2 in human PBMC derived T cells for CAR-T transduction and ACT

The transcription factor IRF2 is a feedback nexus transforming the pro-inflammatory effects of IFN-I into suppressive signaling



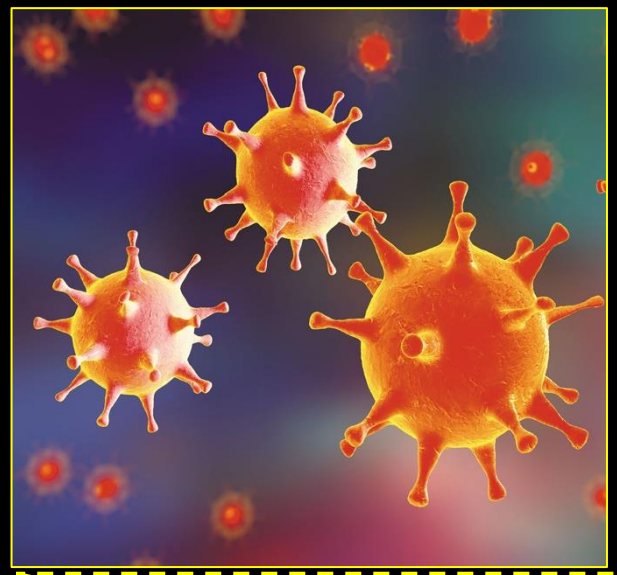
IRF2 modulates IFN-induced gene expression programs associated with exhaustion but not all IFN-induced ISGs.

The transcription factor IRF2 is a feedback nexus transforming the pro-inflammatory effects of IFN-I into suppressive signaling

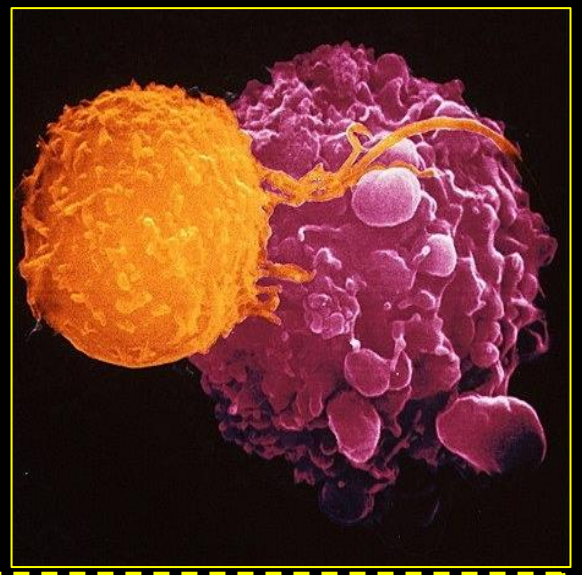


Using viruses and cancer to uncover interferons are positively and negatively regulating immunity

Chronic virus



Cancer



Interferon

Host Immunity

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TIP Tumor Immunotherapy Program

CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

NIH National Institutes of Health

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Canada Leads

The Terry Fox Foundation

Canadian Cancer Society