Analysis of the Interferon Network
8 October 2004
Essigmann

The Players:

IFN:	Interferon
TF:	Transcription Factor
STAT:	Signal Transducers and Activators of Transcription
PK-R:	RNA-activated protein kinase
OAS:	Oligo-A-Synthetase
ADAR:	Adenine Deaminase
IRF:	Interferon Regulatory Factor (TF, or component of a TF)
$IFN_\alpha R_1$	cell surface IFN receptors
$IFN_\alpha R_2$	
$IFN_\alpha R_3$	
JaK and TyK:	Janus Kinases (JaK1, 2, 3; TyK2)
ISRE:	IFN-Stimulated Response Elements (DNA structures)
RNaseL:	endonuclease that cleaves double-stranded RNA of viral genomes

Q: What happens when you get sick?
A: You feel like crap.

White blood cells work better at a higher temperature.
Most pathogens are optimized for body temp.

Feeling like crap = protein synthesis inhibition. Interferons do this.

Properties of IFNs:

a) cytokines: a protein that is produced by cell 1 and acts on cell 2 (and cell 1)
b) proteins ~16-46 Kda (small)
c) glycoproteins
d) have disulfide bonds

Classification of IFNs:

a) by cell surface receptors which they bind
b) by a diagnostic antibody to which they react (historically, antibodies were used as diagnostic reagents

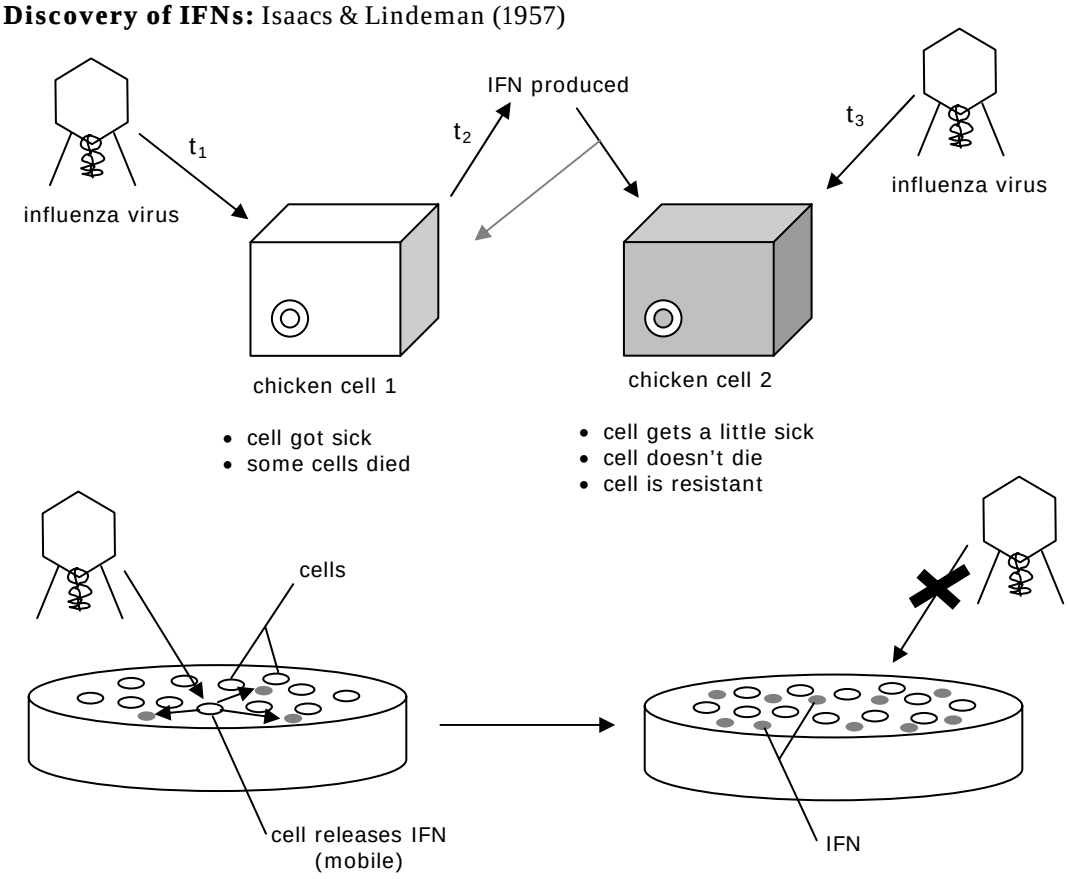
Type I: (by receptor)
IFNα: 14 known polypeptides / 14 genes
IFNβ: 1 peptide / 1 gene
IFNω: 1 protein / 1 gene
IFNτ: 1 gene

Type II: (by receptor)
IFNγ: 1 protein / 1 gene

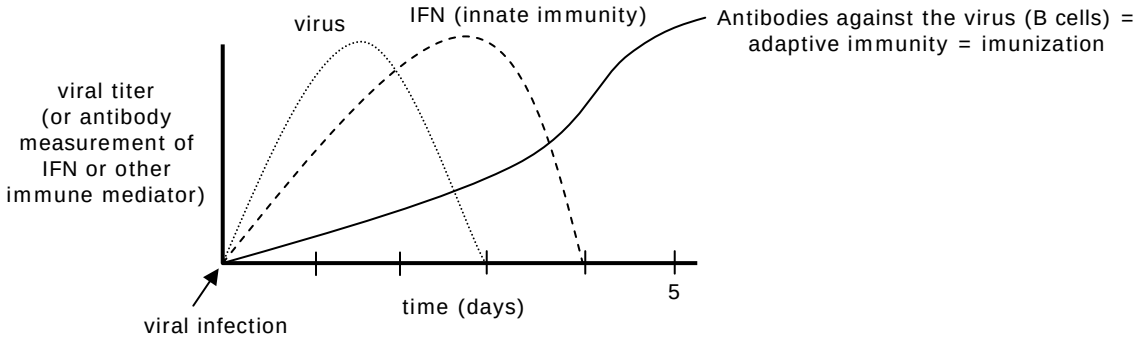
What cells make IFNs?

Type I: almost every cell in the body
Type II: immune system cells (T-cells, NK)

Discovery of IFNs: Isaacs & Lindeman (1957)



What's going on?



→ Interferon sort of "teaches" the B cells what to look for.

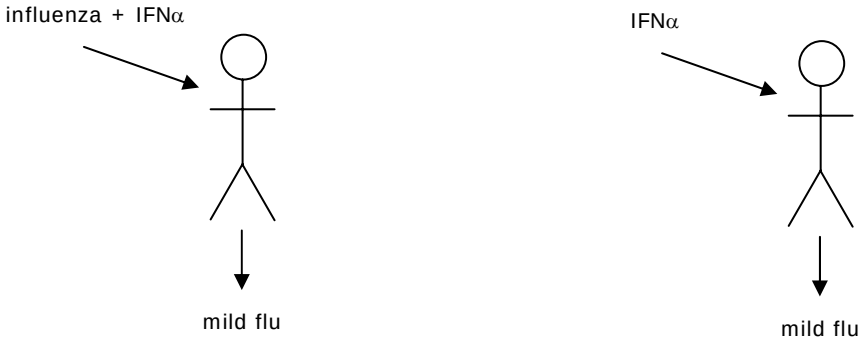
Why did Chiron shut down their flu vaccine plant?

Quality control on purity of the product important to the FDA.
How flu vaccine is made: Room the size of a football field full of 400,000 fertilized chicken eggs. Inject virus into the eggs, suck off fluid, purify a bit, inactivate, inject into humans.

IFN in the world of Biotech:

After the 1957 experiment, people started thinking, "If I had this stuff, I could sell it and make a fortune!" However, when biotech was a budding industry, there were a limited number of proteins they had to work with.

Biogen started clinical trials on a marketable IFNα to "eliminate the cold":



→ IFNα *is* the symptoms of the flu!

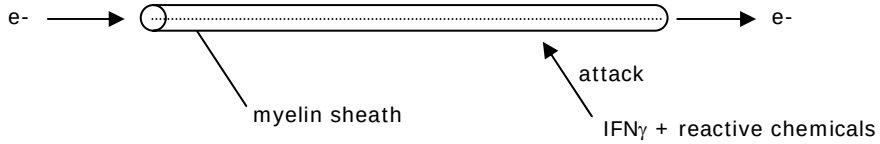
Uses of IFN:

IFNα:

a) common cold (not so good...)
b) hairy cell leukemia (Gutterman) – this is what made IFNα into a multi-billion-dollar market
c) other cancers (colon, melanoma, lung, renal cell, Karposi sarcoma...)
d) viral diseases (e.g. hepatitis C) – currently there's a huge hepC problem in Japan because of a contaminated immunization process)

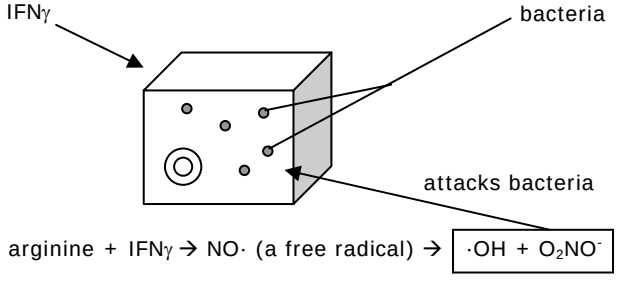
IFNβ:

a) anticancer properties (squam. carcinoma)
b) multiple sclerosis (primary use)
   MS causes the immune system to attack nerves' myelin shealth. IFNβ blocks the action of IFNγ, which is believed to be what's attacking the myelin.



IFNγ: (Type II)

a) chronic granulomatosis disease



b) Leishmanaisis (a parasitic disease)
c) idiopathic pulmonary fibrosis (like Crohn's disease of the airways)

Let's look at the progression of a cold on three different timescales: