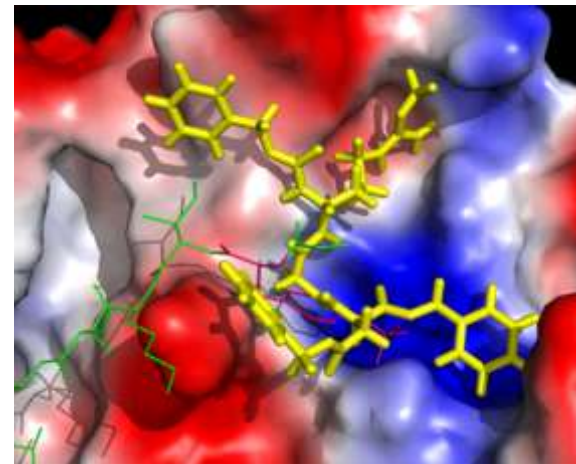
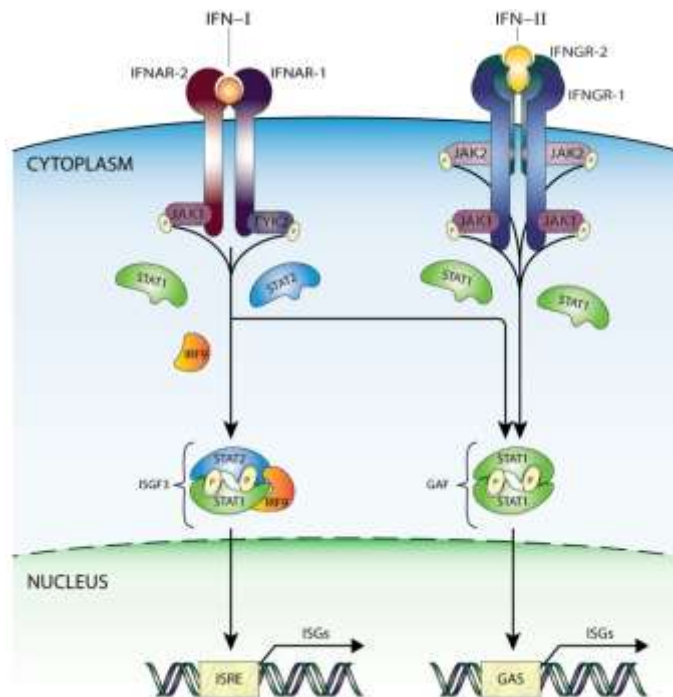
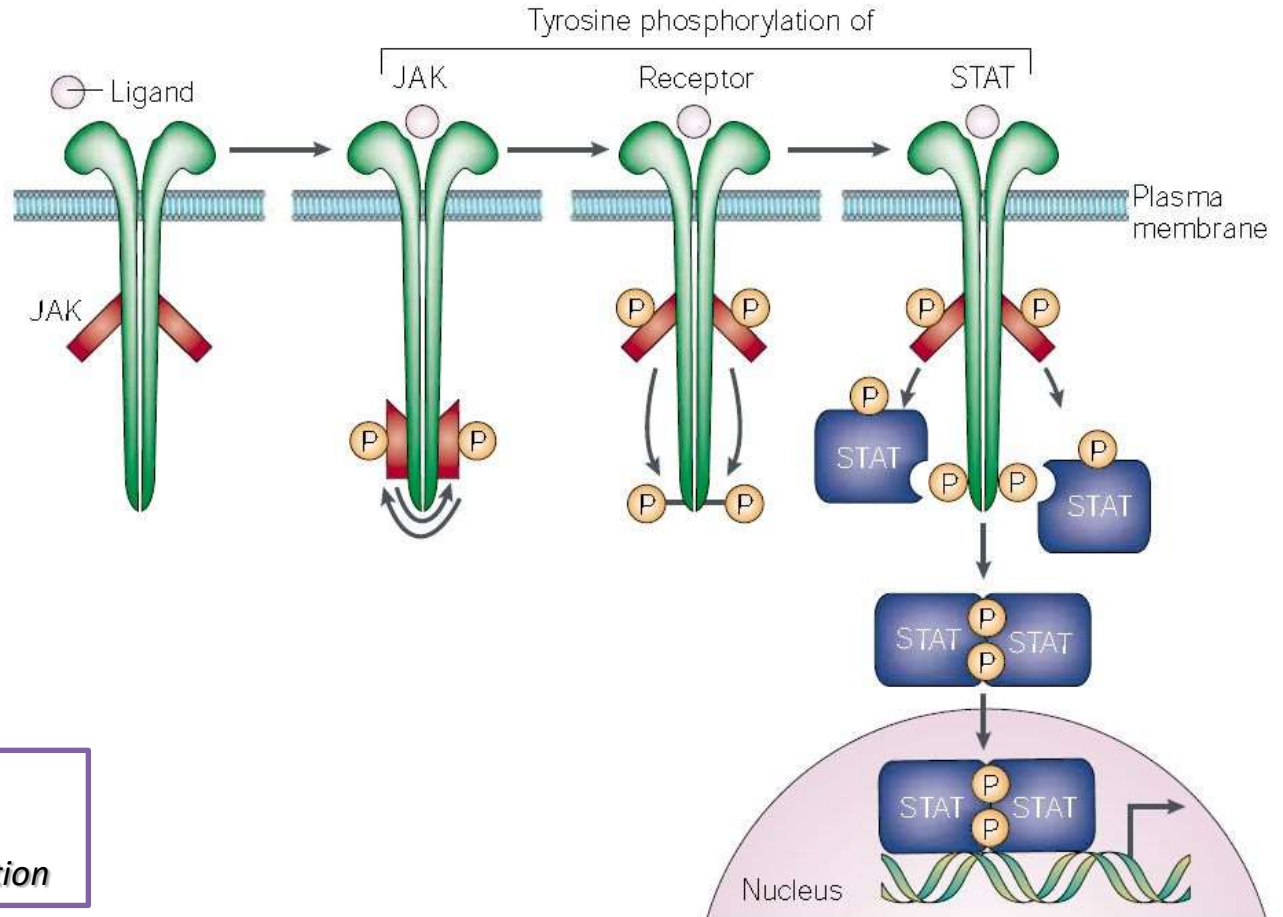


# STATs in Inflammation & Cancer



Prof. Hans Bluysen  
Lab Human Mol Genetics  
09-02-2021

# Canonical JAK-STAT pathway



**JAK** - Janus Kinase  
**STAT** - Signal Transducer and Activator of Transcription

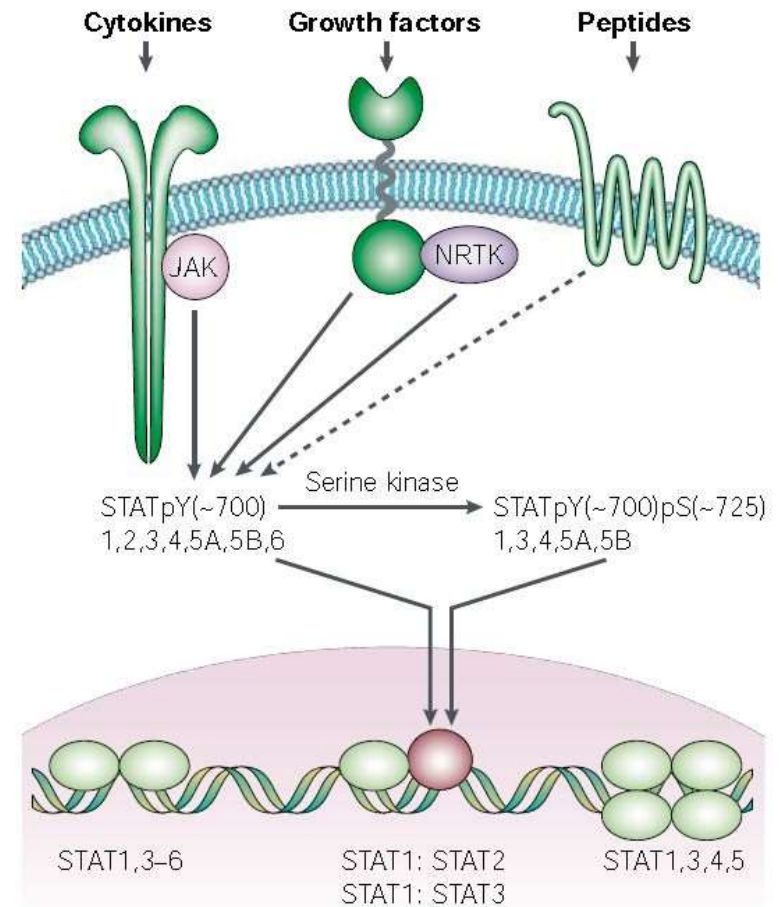
# General triggers of JAK-STAT pathway

Cytokines  
interferons  
interleukines

Growth factors  
EGF  
PDGF

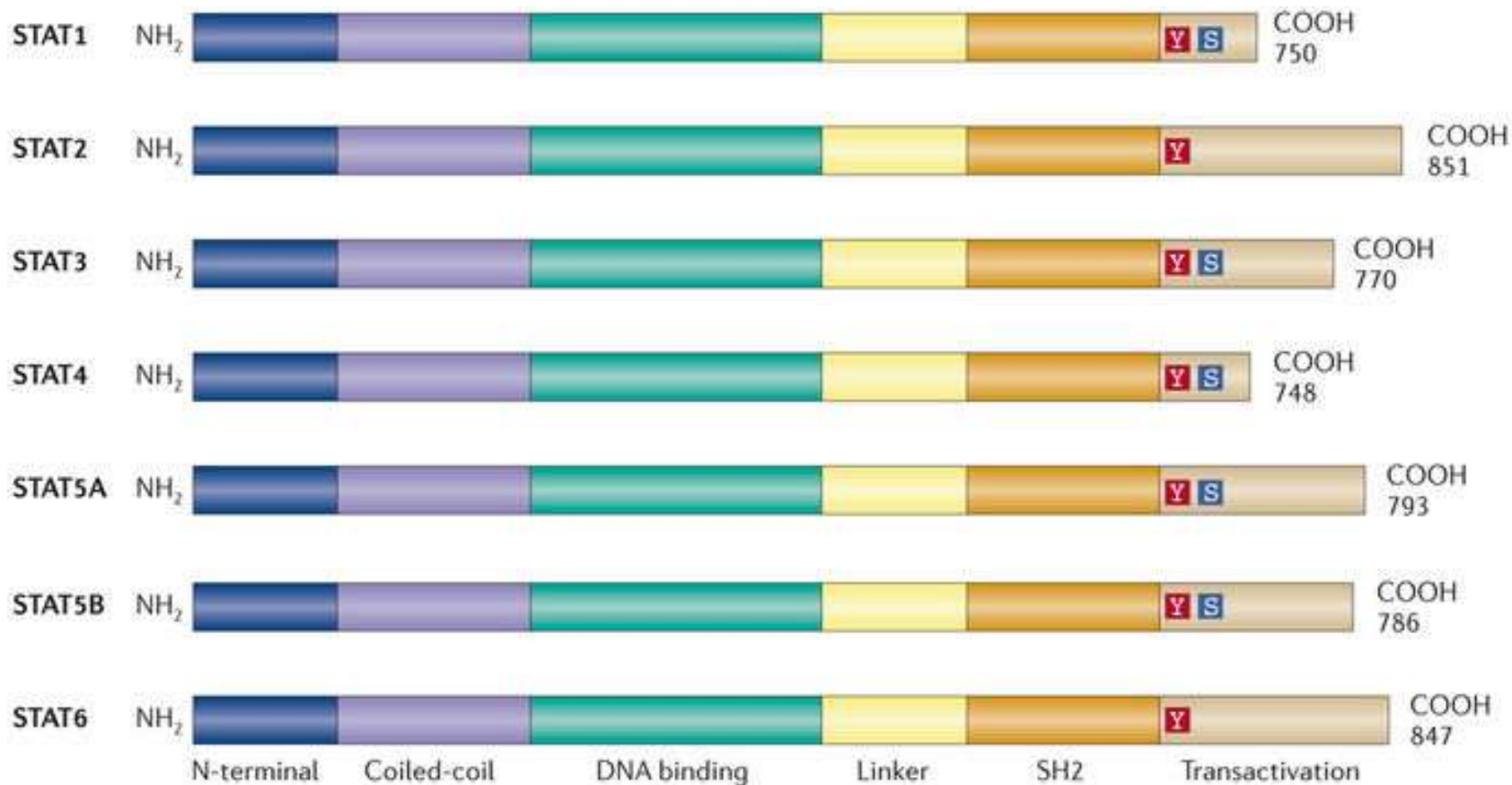
Bacterial molecules  
LPS  
LTA  
dsRNA

Src and Abl kinases  
G-coupled receptors  
AngII

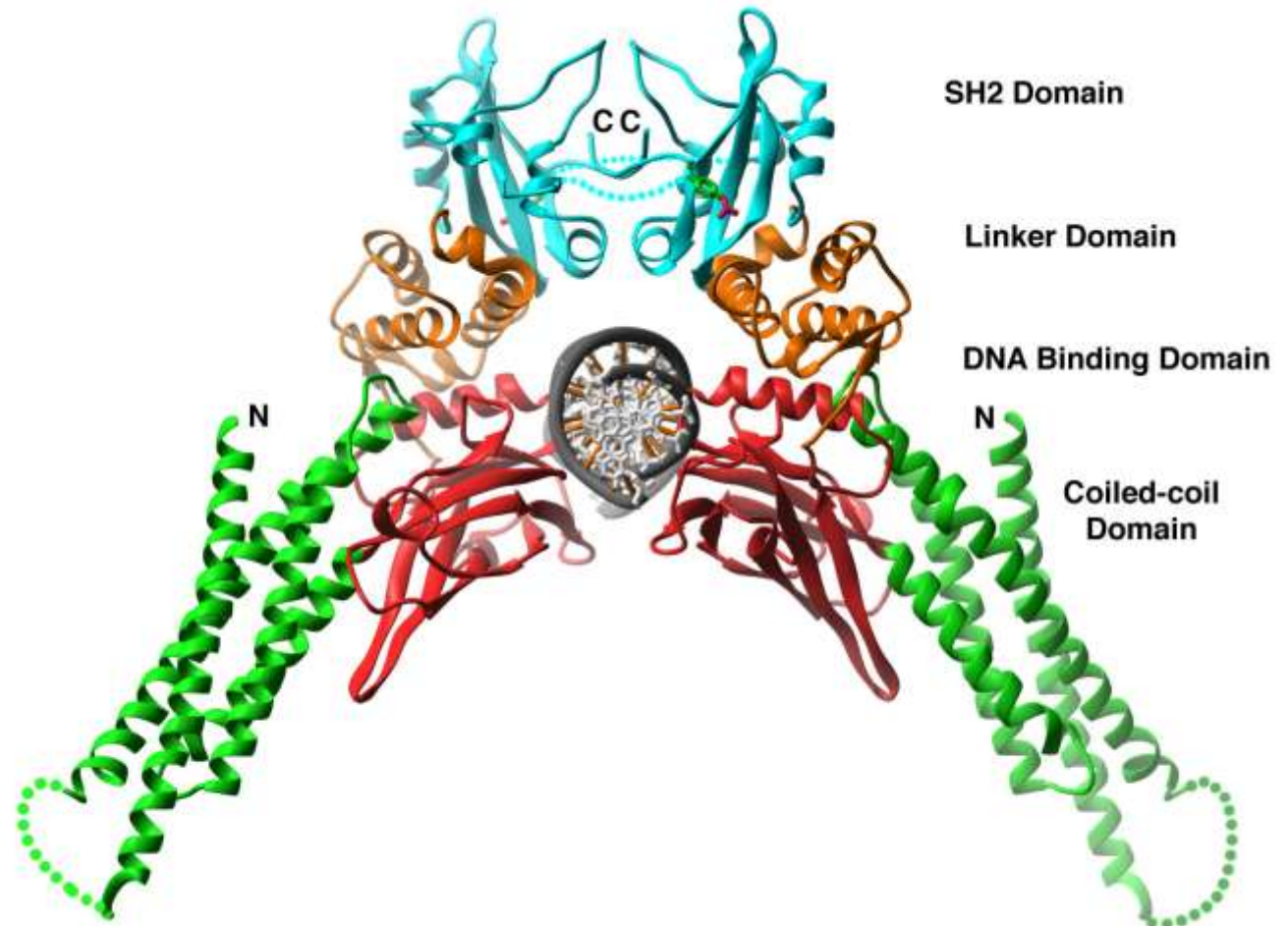




# STAT Family: Structure

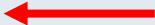


# STAT-DNA Binding





# STATs in Health & Disease

STAT	Cellular functions	Major diseases
1	<ul style="list-style-type: none"><li>• Cell growth and apoptosis</li><li>• T<sub>H</sub>1 cell-specific cytokine production</li><li>• Antimicrobial defence</li></ul>	<ul style="list-style-type: none"><li>• Atherosclerosis</li><li>• Infection</li><li>• Immune disorders</li></ul>
2	<ul style="list-style-type: none"><li>• Mediation of IFN<math>\alpha</math>/IFN<math>\beta</math> signalling</li></ul>	<ul style="list-style-type: none"><li>• Cancer</li><li>• Infection</li><li>• Immune disorders</li></ul>
3	<ul style="list-style-type: none"><li>• Cell proliferation and survival</li><li>• Inflammation</li><li>• Immune response</li><li>• Embryonic development</li><li>• Cell motility</li></ul>	<ul style="list-style-type: none"><li>• Cancer </li></ul>
4	<ul style="list-style-type: none"><li>• T<sub>H</sub>1 cell differentiation</li><li>• Inflammatory responses</li><li>• Cell proliferation</li></ul>	<ul style="list-style-type: none"><li>• Experimental autoimmune encephalomyelitis (multiple sclerosis)</li><li>• Systemic lupus erythematosus</li></ul>
5A	<ul style="list-style-type: none"><li>• Cell proliferation and survival</li><li>• IL-2R<math>\alpha</math> expression in T lymphocytes</li><li>• Mammary gland development</li><li>• Lactogenic signalling</li></ul>	<ul style="list-style-type: none"><li>• Cancer</li><li>• Chronic myelogenous leukaemia</li></ul>
5B	<ul style="list-style-type: none"><li>• Cell proliferation and survival</li><li>• IL-2R<math>\alpha</math> expression in T lymphocytes</li><li>• Sexual dimorphism of body growth rate</li><li>• NK cell cytolytic activity</li></ul>	<ul style="list-style-type: none"><li>• Cancer</li><li>• Chronic myelogenous leukaemia</li></ul>
6	<ul style="list-style-type: none"><li>• Inflammatory and allergic immune response</li><li>• B cell and T cell proliferation</li><li>• T<sub>H</sub>2 cell differentiation</li></ul>	<ul style="list-style-type: none"><li>• Asthma</li><li>• Allergy</li></ul>



# STAT3: A target for many human cancers

50-90% STAT3 activation in:

## *Solid Tumors*

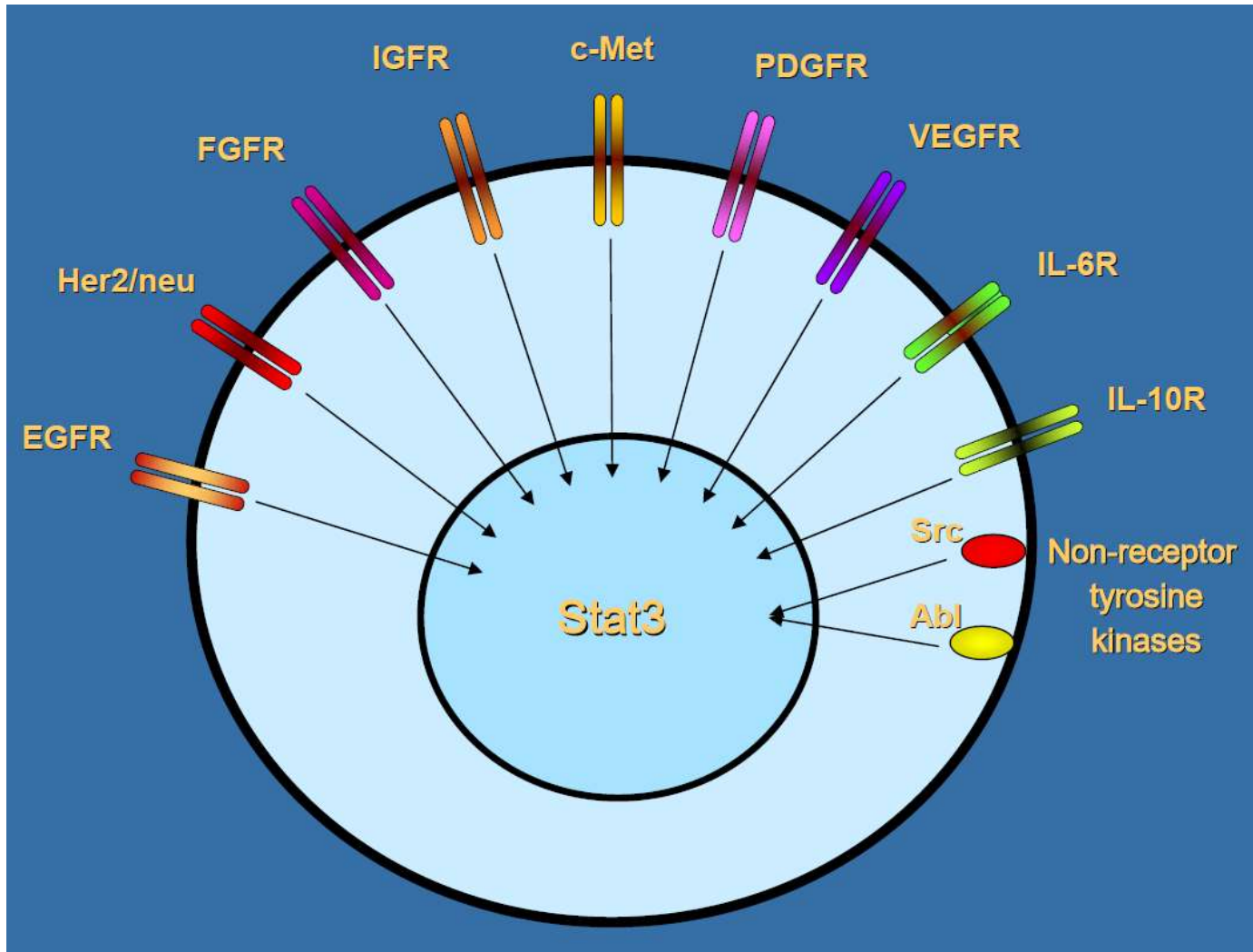
Prostate cancer	STAT3
Non-small Cell Lung cancer	STAT3
Breast cancer	STAT3, STAT5
Head and Neck cancer	STAT3
Melanoma	STAT3
Ovarian cancer	STAT3
Pancreatic cancer	STAT3
Glioma	STAT3
Stomach Cancer	STAT3
Cervical Cancer	STAT3

## *Blood Tumors*

Multiple Myeloma	STAT3
Acute Myelogenous Leukemia (AML)	STAT3, STAT5
Chronic Myelogenous Leukemia (CML)	STAT5
Burkitt's Lymphoma	STAT3
Non-Hodgkins Lymphoma	STAT3
Cutaneous T cell Lymphoma	STAT3

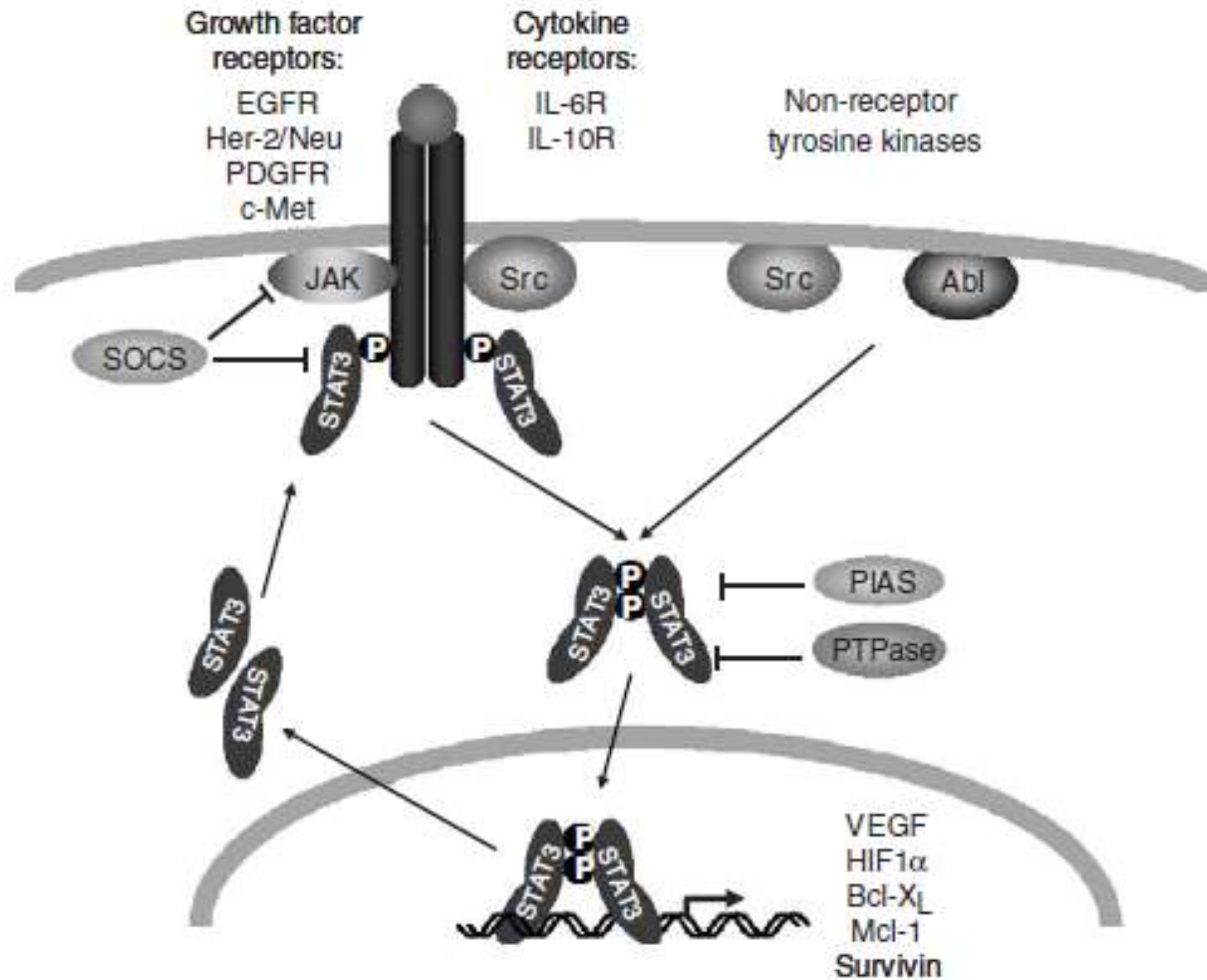


# STAT3: Point of convergence in oncogenic signaling



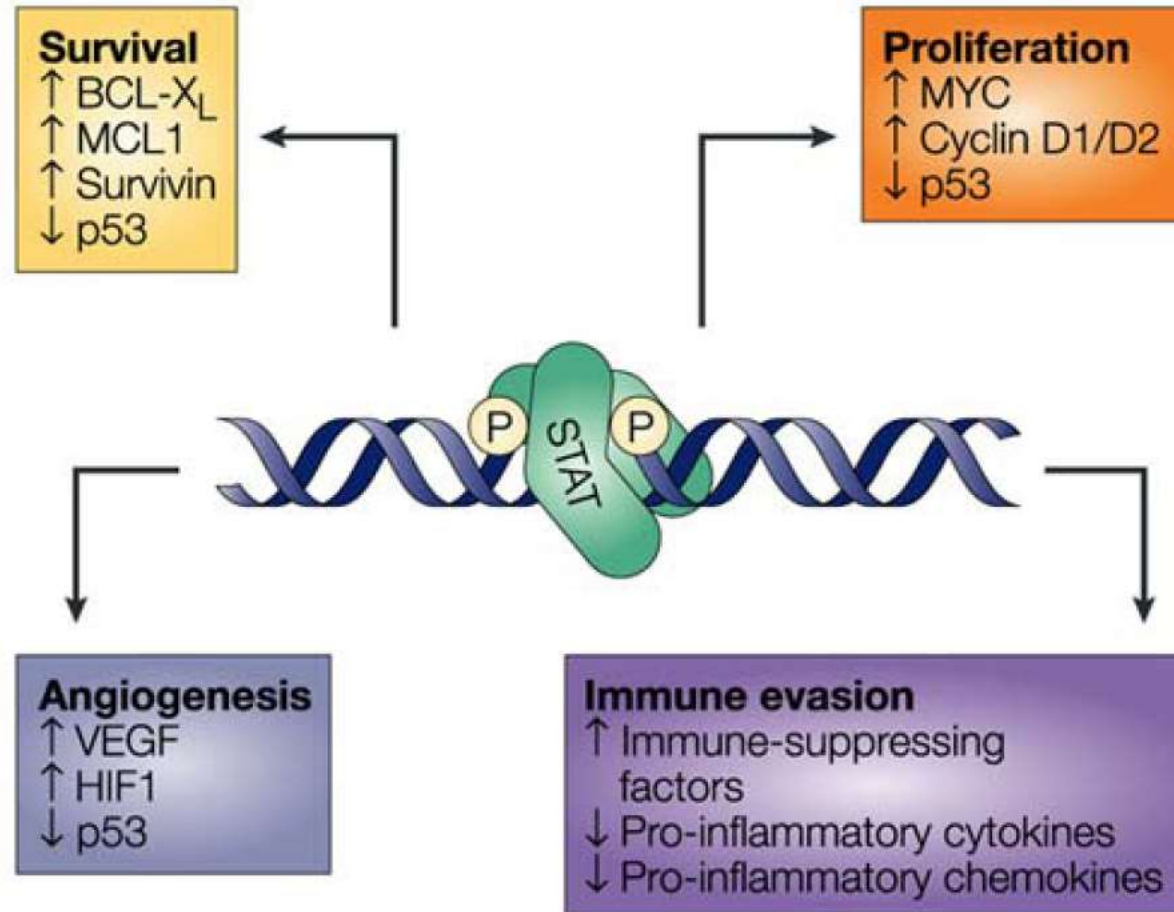


# STAT3 activation in Cancer



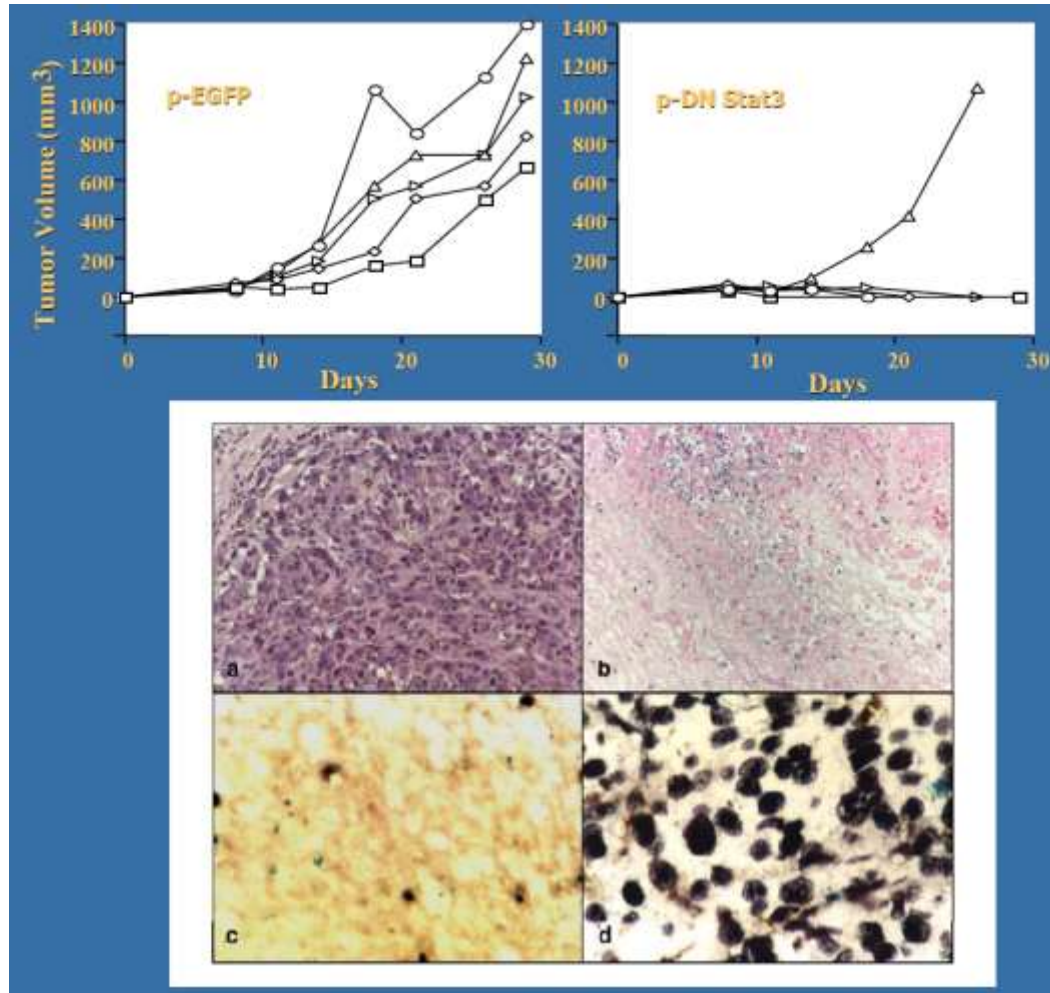


# Multiple roles of STAT3 activation in tumor cells





# Gene therapy with DN-STAT3 Involves “Bystander effects”



Murine Melanoma  
B16 Tumors

15% electroinjected

50-90% apoptotic

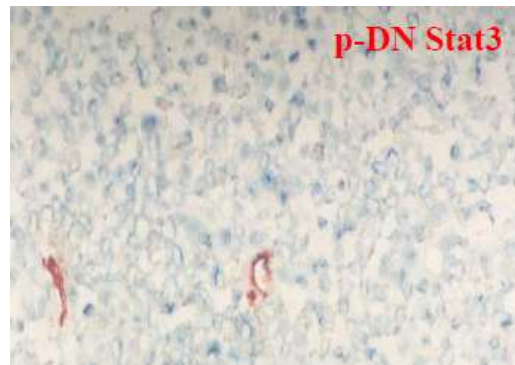
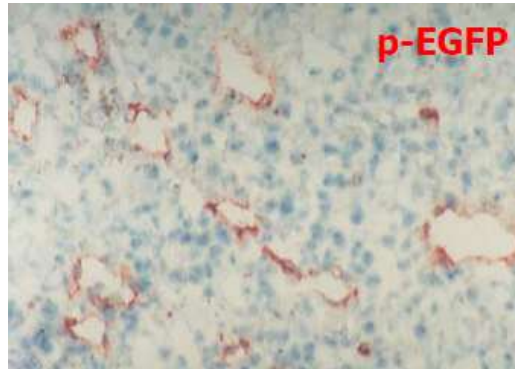
Influx immune cells

pEGFP

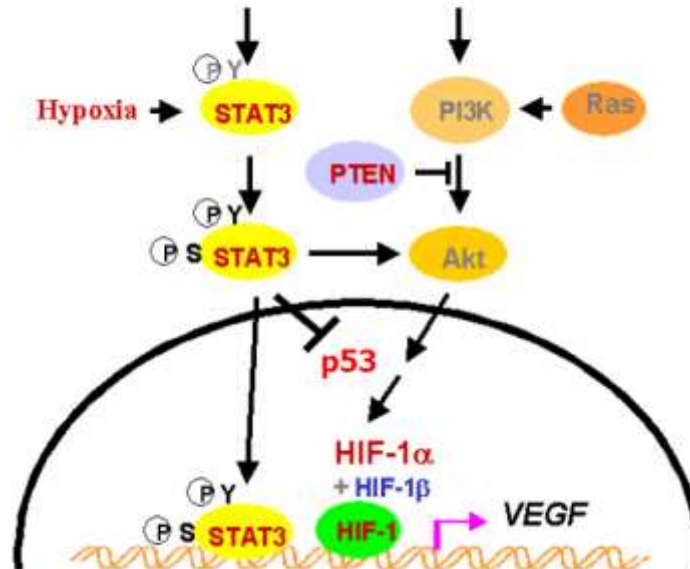
pDN-STAT3

*Niu et al., 1999*

# STAT3 is critical for Tumor Angiogenesis



Src, EGFR, HER2/neu, PDGFR, IL-6...



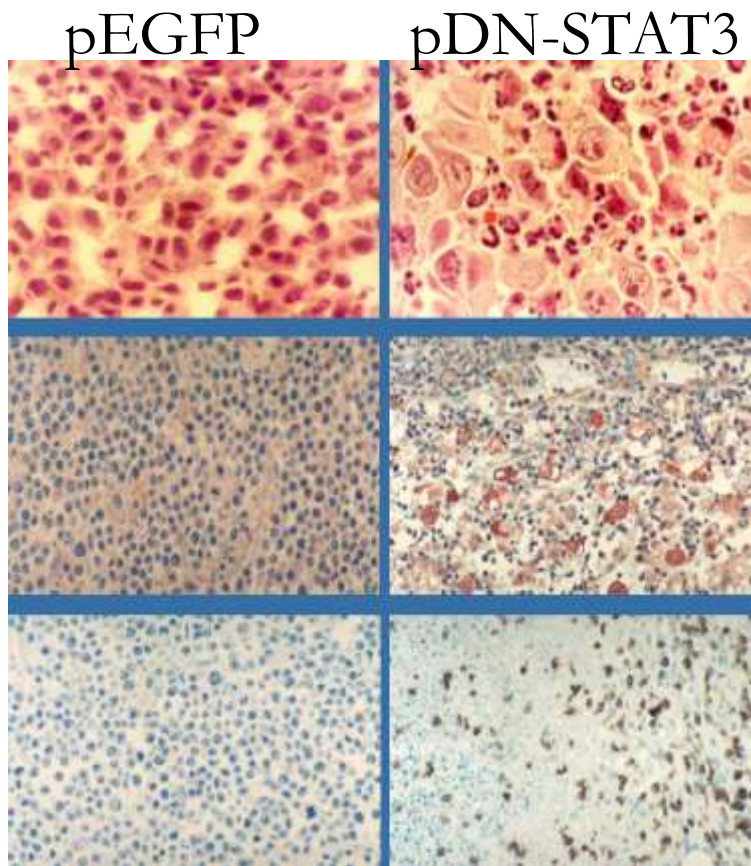
## Angiogenesis

- |         |                |
|---------|----------------|
| ↑ VEGF  | ↓ IFN $\gamma$ |
| ↑ bFGF  | ↓ IL-12        |
| ↑ HGF   | ↓ IP-10        |
| ↑ HIF-1 | ↓ Stat1        |
| ↑ MMP-2 | ↓ IFN $\beta$  |
| ↑ MMP-9 | ↓ p53          |

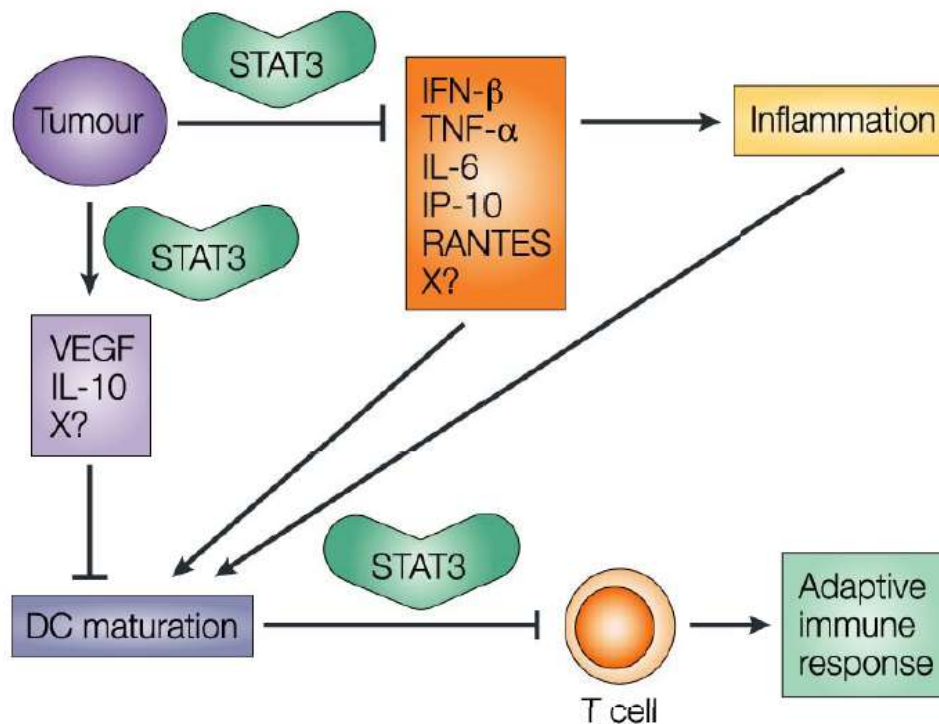
Niu et al, *Oncogene*, 21:2000-2008, 2002  
 Xu et al, *Oncogene*, 25:5552-5560, 2005  
 Niu et al, *Mol Cell Biology*, 25, 7432-7440, 2005



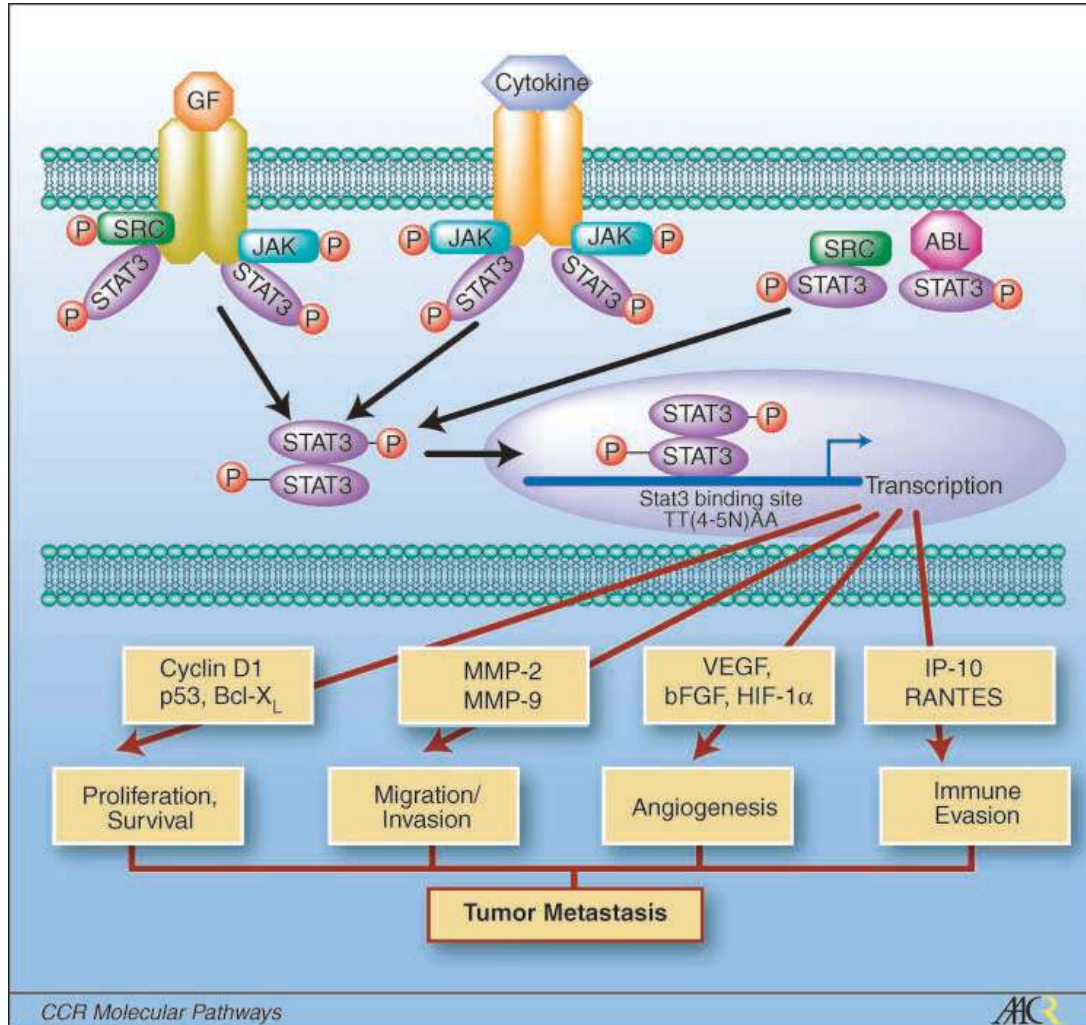
# Critical role of tumor STAT3 Activation in Immune Evasion



Influx of immune cells  
Increased apoptosis



# Role of STAT3 in Oncogenesis & Tumor Metastasis



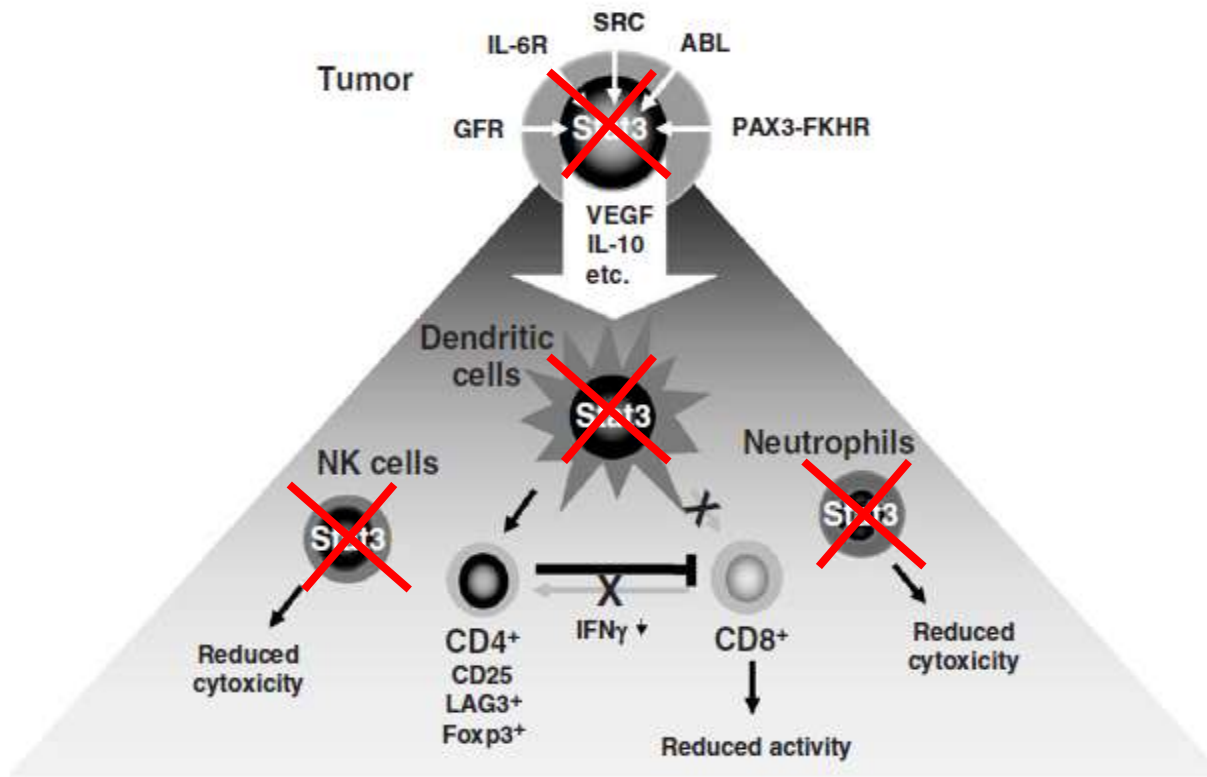
STAT3:  
a novel multi-functional protein involved in

tumor development  
tumor progression  
tumor-induced immuno  
suppression  
metastasis

in different types of cancer.

# STAT3 in Cancer

## Solid Tumors



Inhibition of tumor **development + progression**

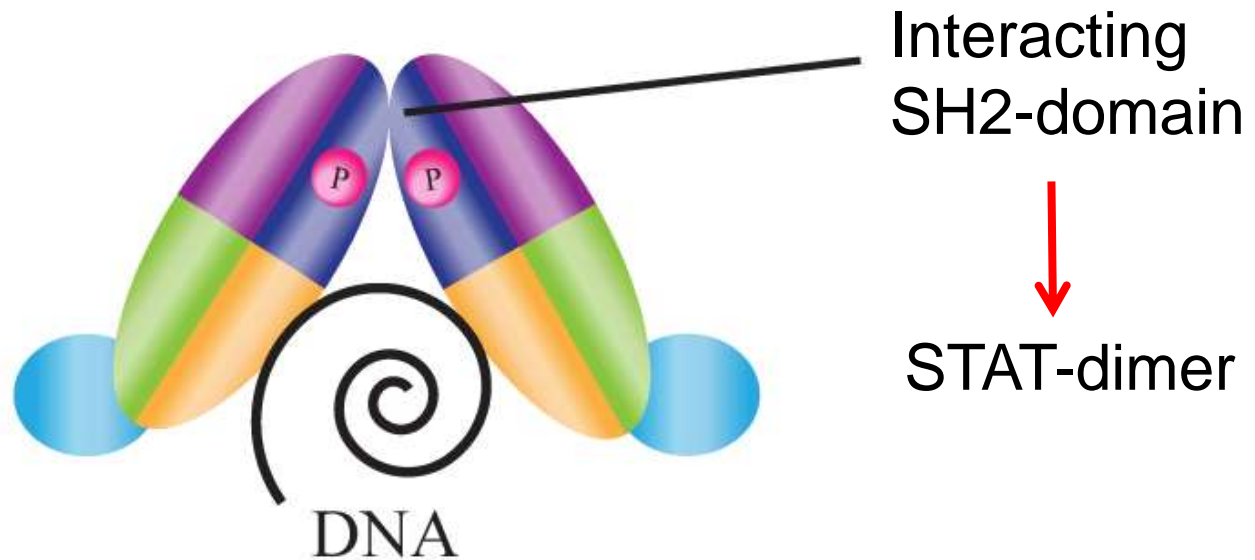
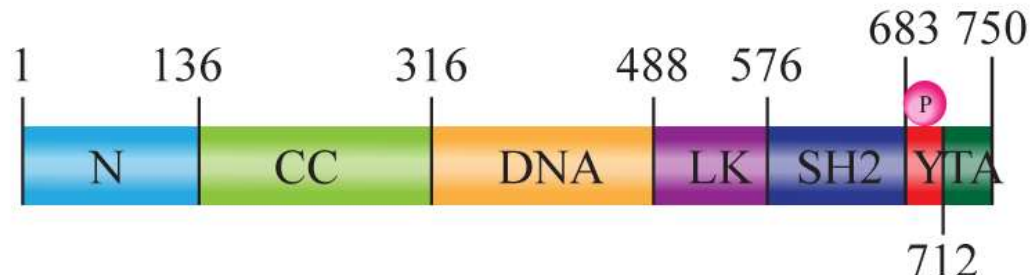
- Small molecule inhibitors  
compounds  
phosphopeptides  
peptidomimetics

- Gene therapy  
DN-STAT3  
SOCS3

- RNAi + targeting  
vectors

- Combination therapy  
Immune therapy

# STAT Structure & Dimerization



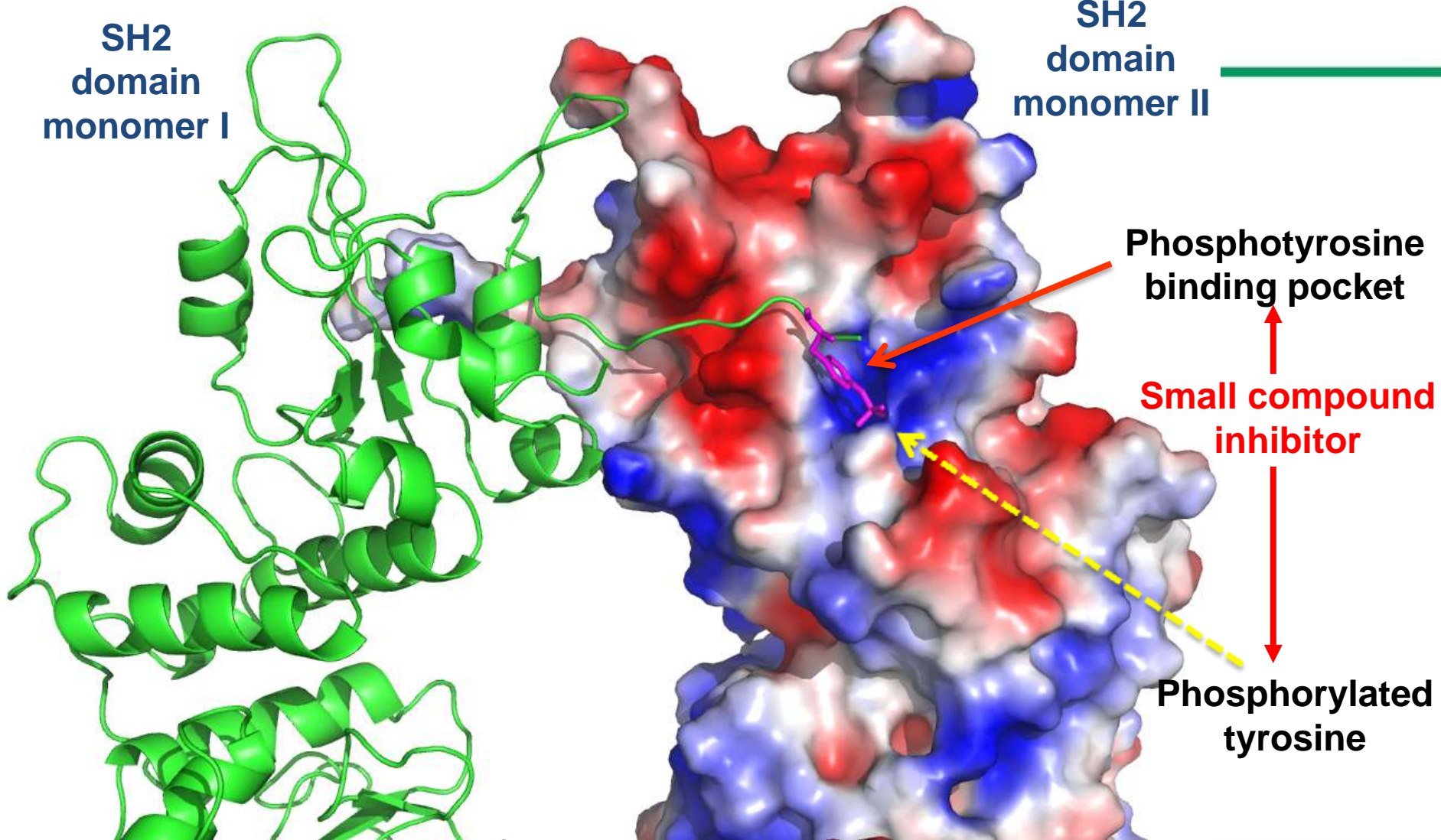




# Structural information: STAT1-STAT3

SH2  
domain  
monomer I

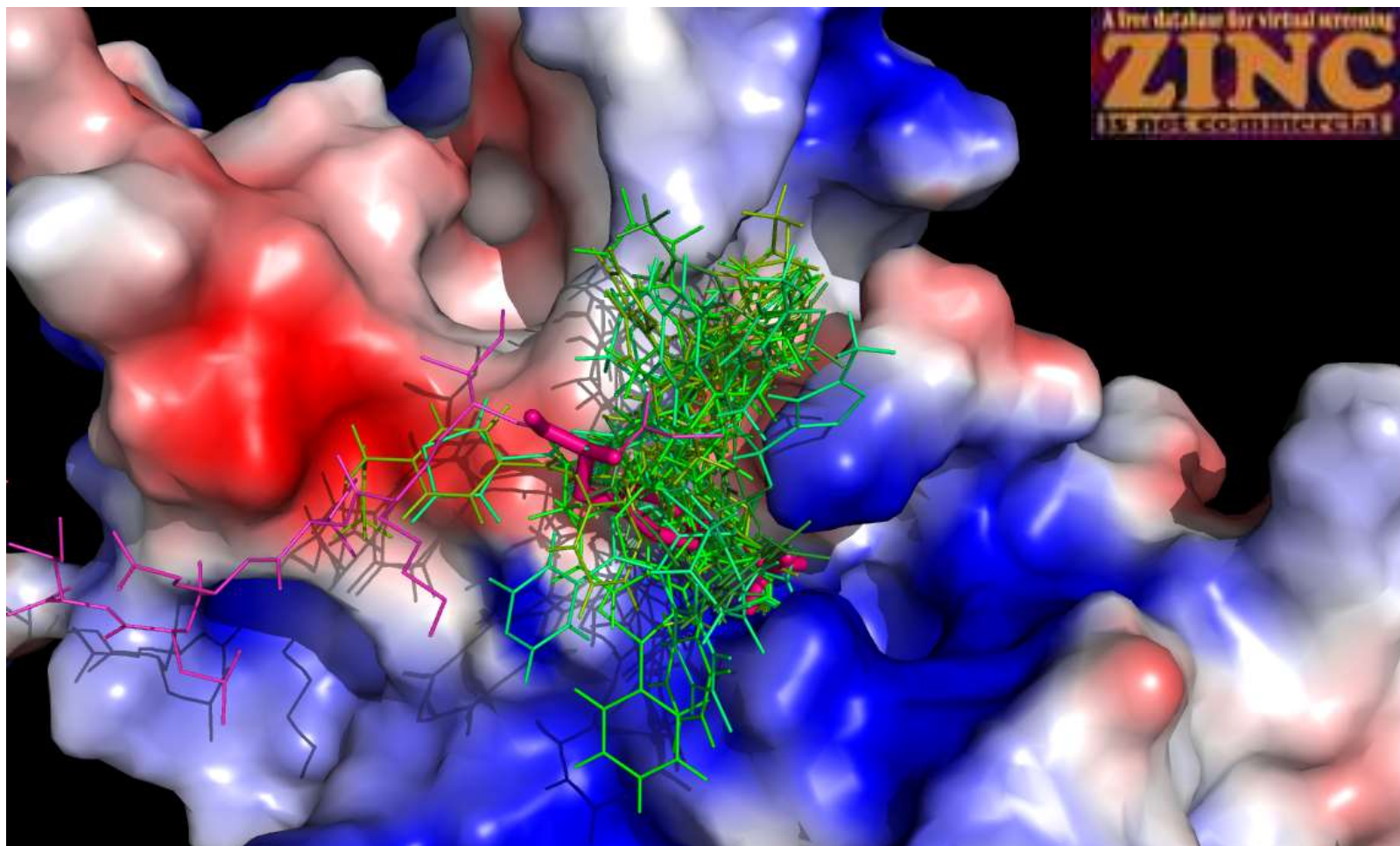
SH2  
domain  
monomer II





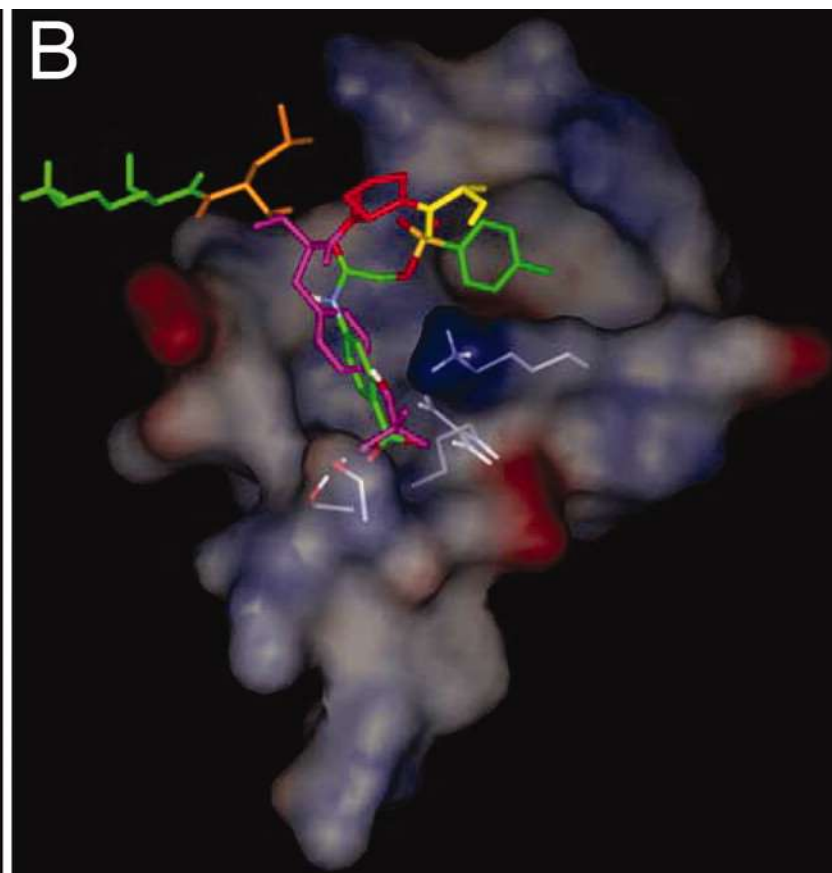
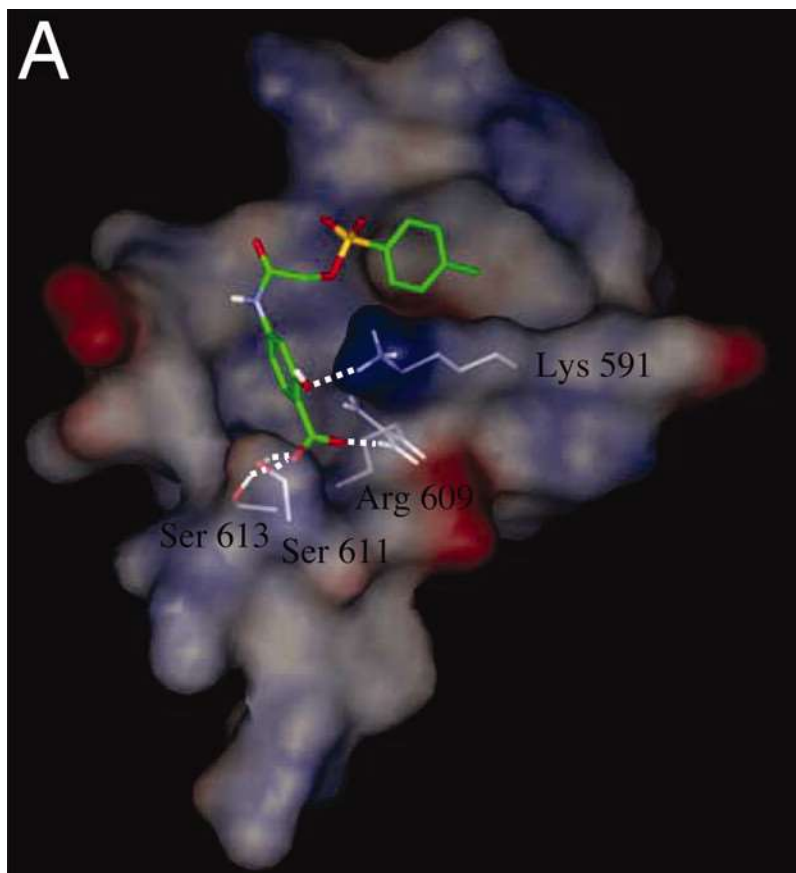
# Novel STAT Inhibitors: Virtual Screening

HSTAT1-SH2 model



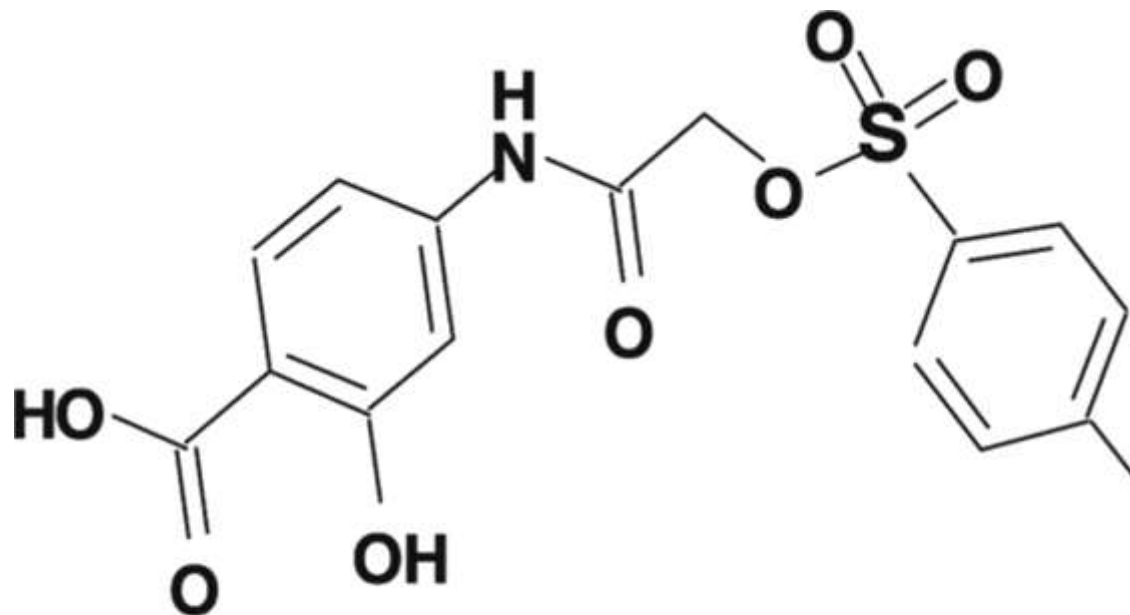


# Application of computational modelling in virtual screening to identify the compound S3I-201 from a chemical database





# STAT3 inhibitory compound



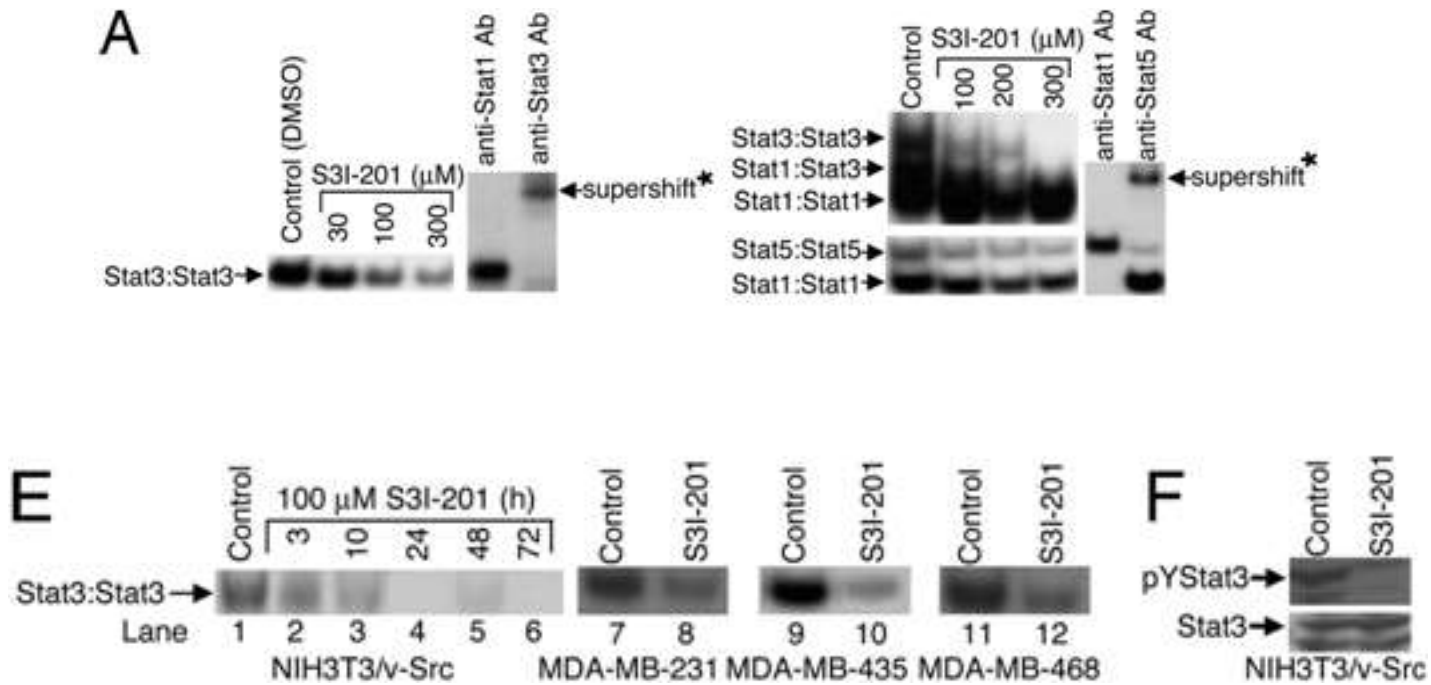
Dimerization

DNA binding

**NSC 74859 (S3I-201)**



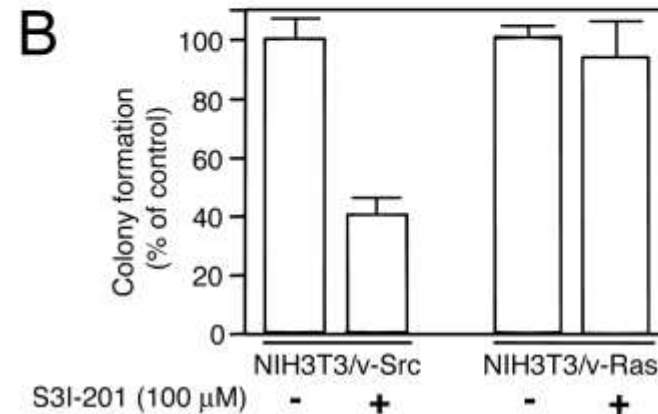
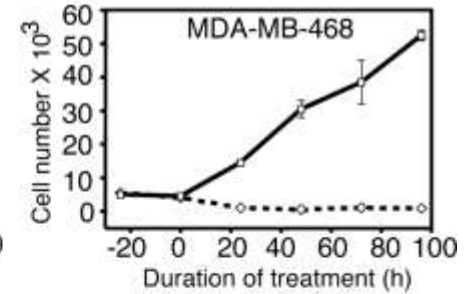
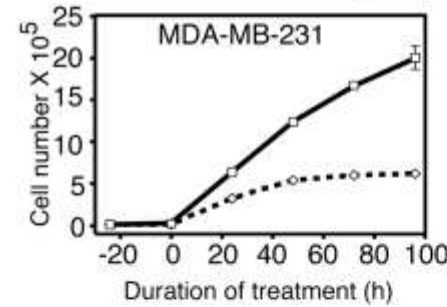
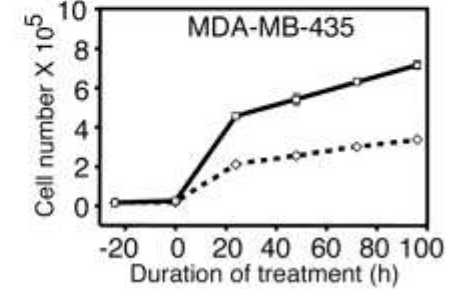
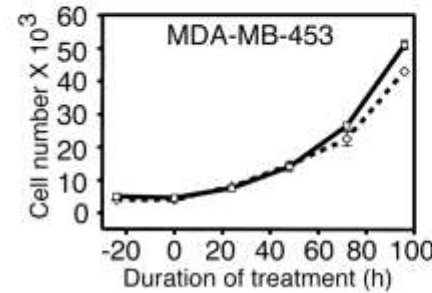
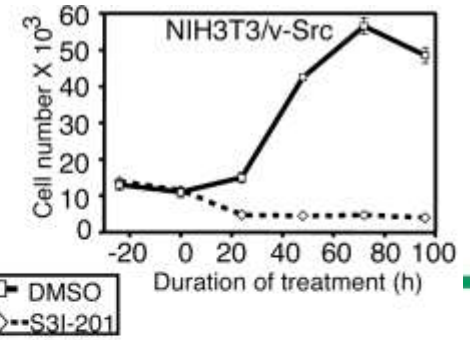
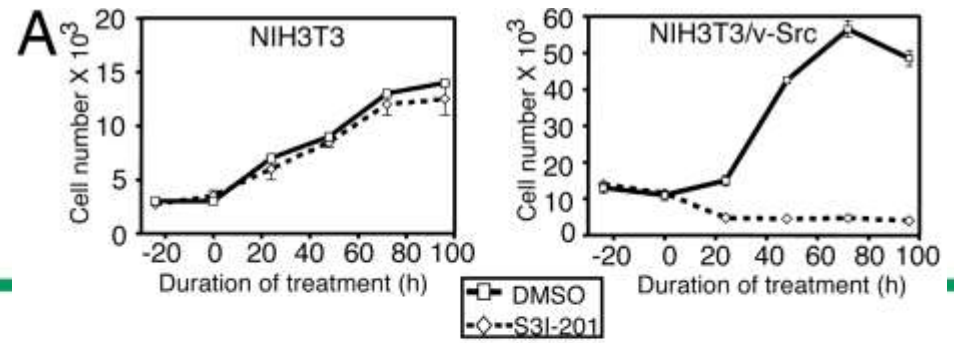
# Evaluation for effects of S3I-201 on STAT-DNA binding



*Siddiquee K. et al. PNAS 2007;104:7391-7396*



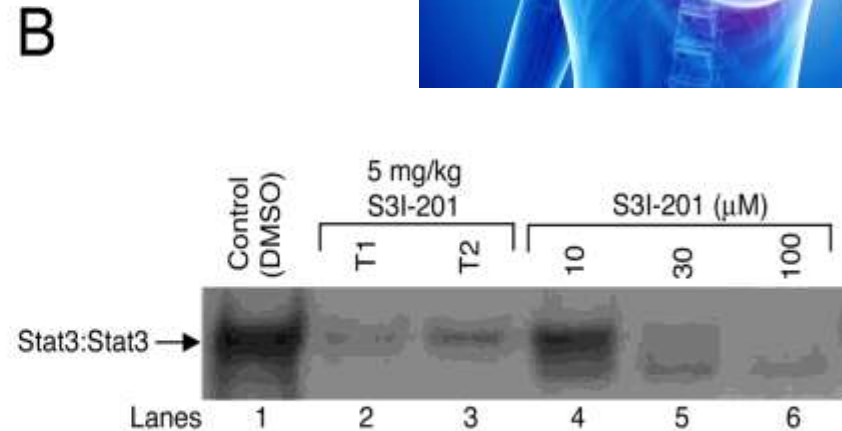
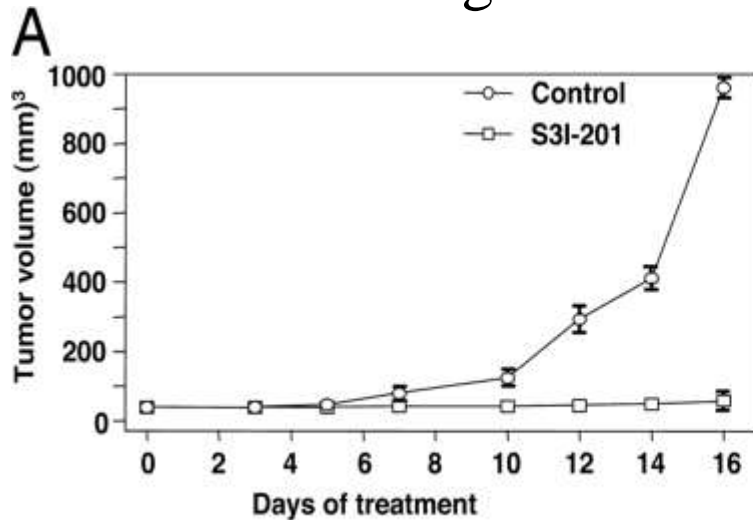
# S3I-201 inhibits anchorage-dependent and -independent growth only of cells that contain persistently active Stat3





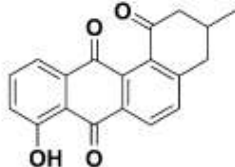
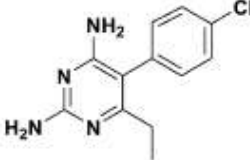
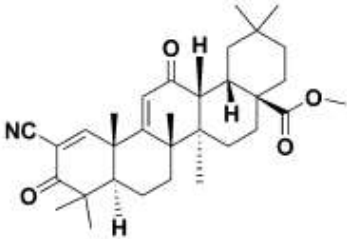
# In vivo Tumor growth inhibition by S3I-201

Human breast (MDA-MB-231)  
tumor-bearing mice



# STAT3 inhibitors in clinical trials

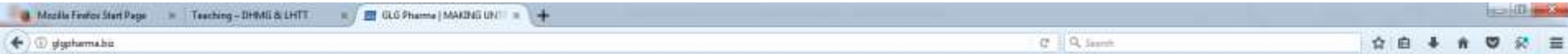
Table 9. Stat3 Inhibitors in Clinical Trials

Agent	Structure	Trial phase	Indication	References
<b>1</b>		Phase I/II	Psoriasis	142
Pyrimethamine		Phase I/II	Chronic lymphocytic leukemia / Small lymphocytic lymphoma	143
OPB-31121	Structure not disclosed	Phase I	Advanced solid tumor	144
<b>53</b>		Phase I/II  Phase II	Pancreatic cancer  Solid tumors and lymphoid malignancies	145  146





# GLG Pharma



GLG

PLSKA

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MAKING UNTREATABLE DISEASES TREATABLE

## STAT3 INHIBITORS

GLG Pharma's therapies are based on unique small molecules and formulations that inhibit dysfunctional STAT3





## STAT3 Mediated Diseases Result from Uncontrolled STAT3 Activation

Activation of STAT3 PROTEIN

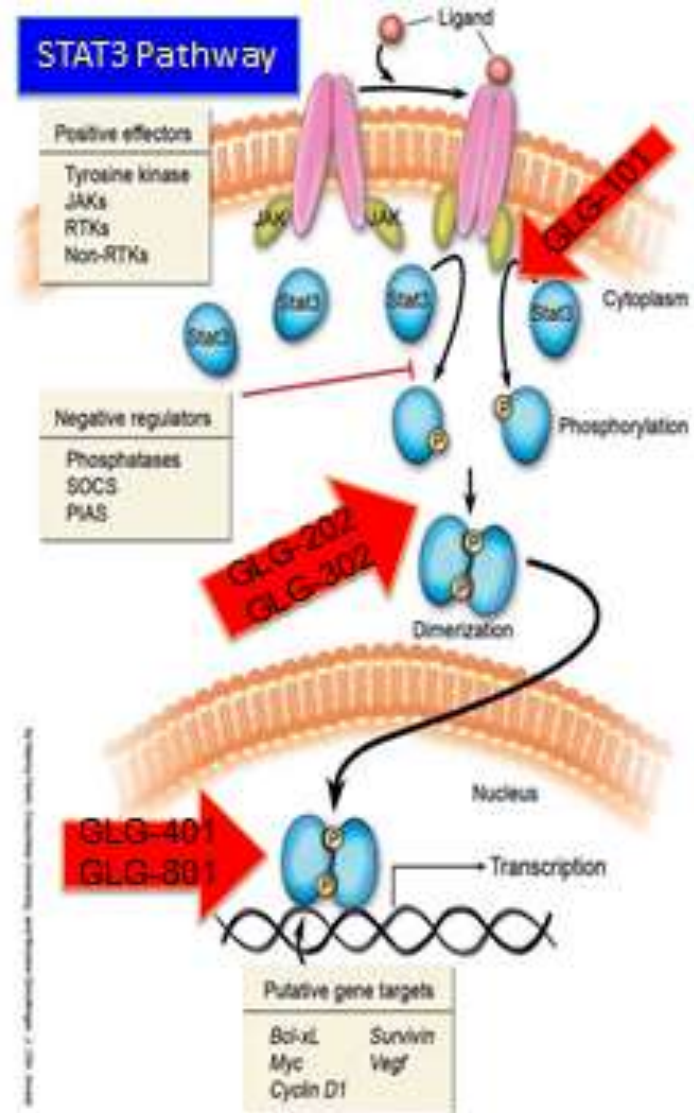
is essential for

- cell growth
- division
- apoptosis

Normal cell: activation is switched on/off by positive effectors & negative regulators

Diseased cell: **switch stays on**, process occurs constantly at high levels, keeping cells growing & dividing uncontrollably

Diseases: Kidney disease, cancer, psoriasis





# GLG Pharma: Pipeline

There are currently 12 STAT3 inhibitors in the GLG Pharma pipeline.

Phase II clinical trials are currently underway with GLG-801 for chronic lymphatic leukemia (CLL). It is anticipated that Phase II studies will be completed in 2016 and Phase III clinical trials will begin in 2017 in the United States, Poland, Germany and France.

Pre-clinical work on GLG-801 has been completed for polycystic kidney disease and Phase I clinical trials are planned for 2016.

Pre-clinical work on GLG-302 for the treatment of triple negative breast cancer (TNBC) has been completed. Phase I clinical trials are planned for 2016.

A number of toxicity studies are being completed for several indications

A unique diagnostic tool has been developed to identify promising candidates for STAT3 inhibitor therapy and monitor patient's progress.

Because there is no current effective treatment for these diseases, regulatory approval processes should be accelerated

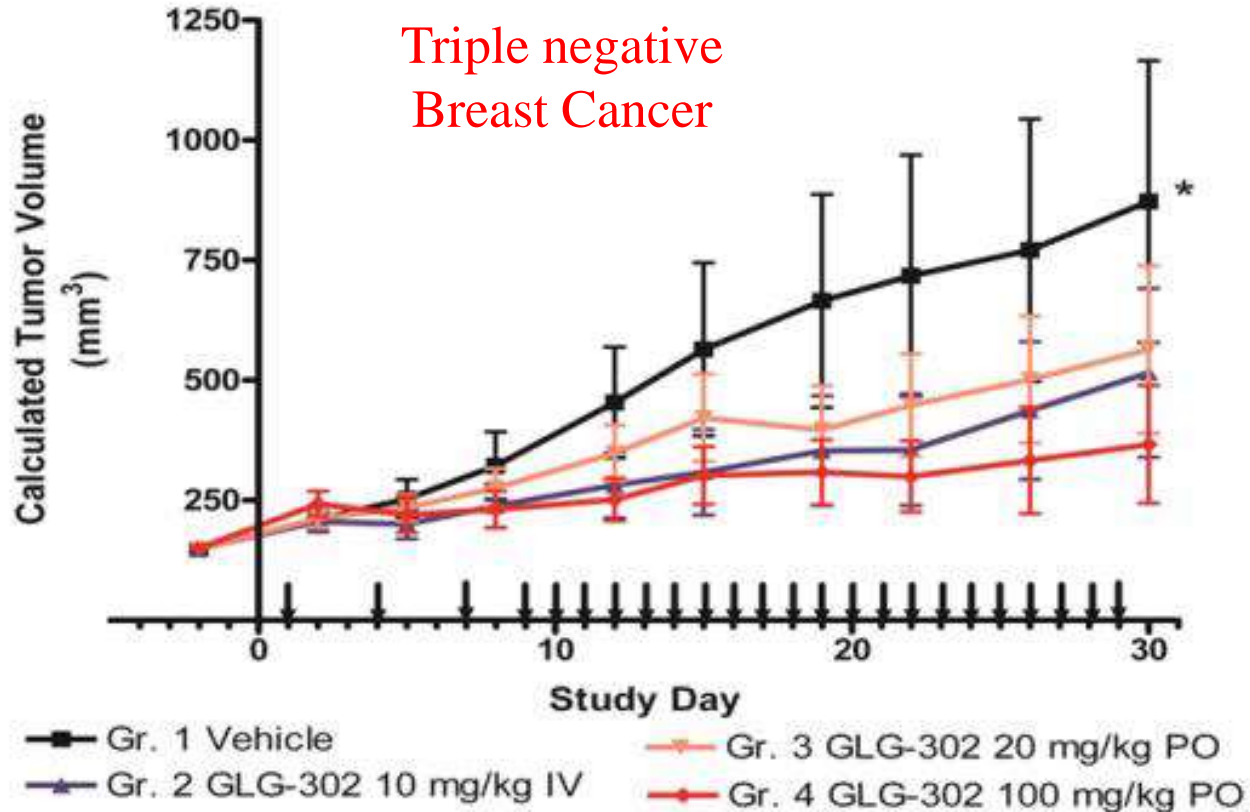




# GLG Pharma: Pipeline

0711-GLG-011 (BTS 11175-02)

MDA-MB-231 Xenograft Study Examining GLG-302, IV or PO vs Vehicle  
Group Average of Individual Calculated Tumor Volume

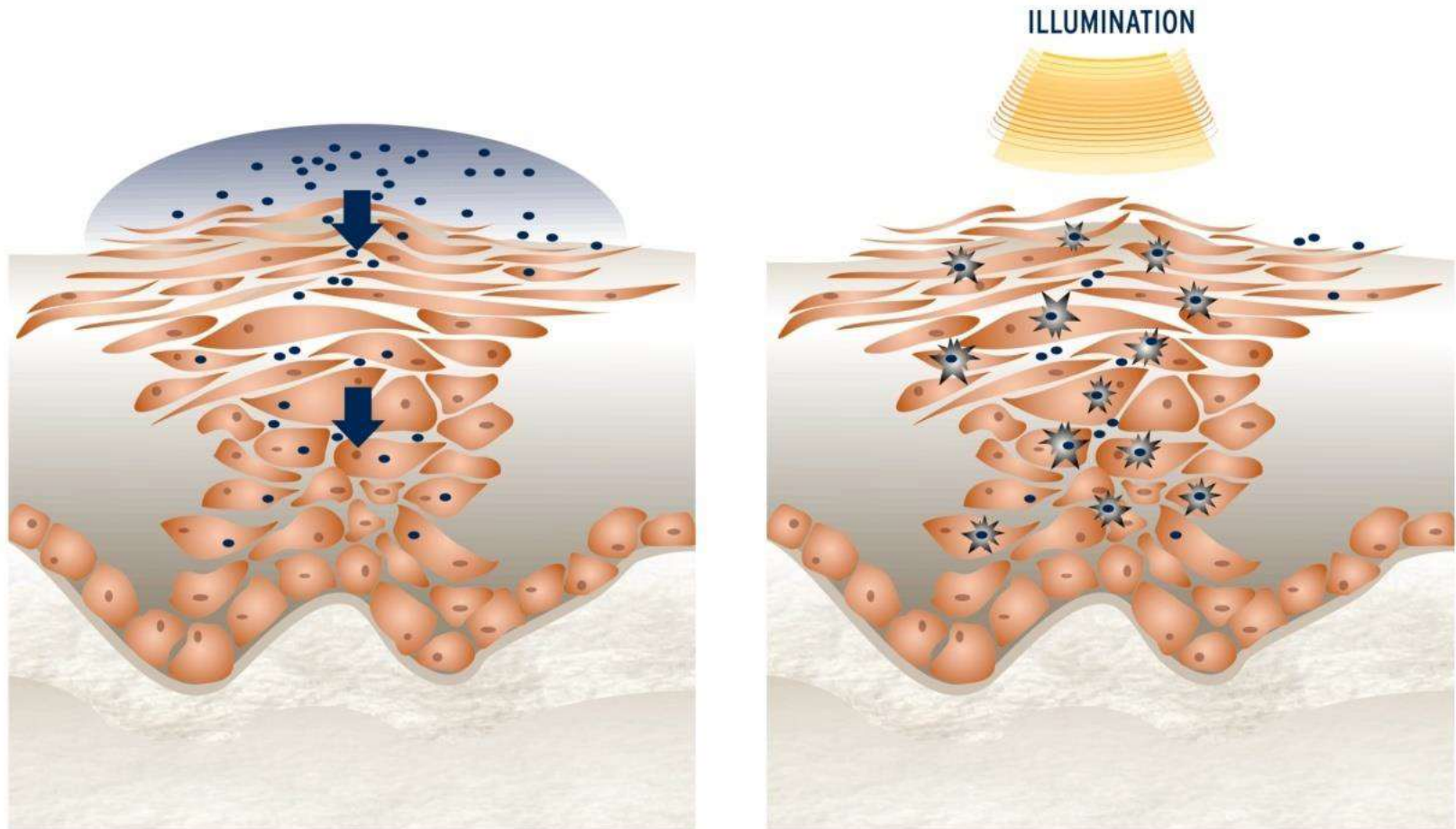


↓ = Day of TA Administration

\* n = 9, single animal euthanized on Day 26 (post tumor measurement), per protocol and IACUC, due to excessive tumor size (> 2000 mm<sup>3</sup>; actual 2577 mm<sup>3</sup>), animal data was carried forward for analysis



# GLG Pharma: Pipeline

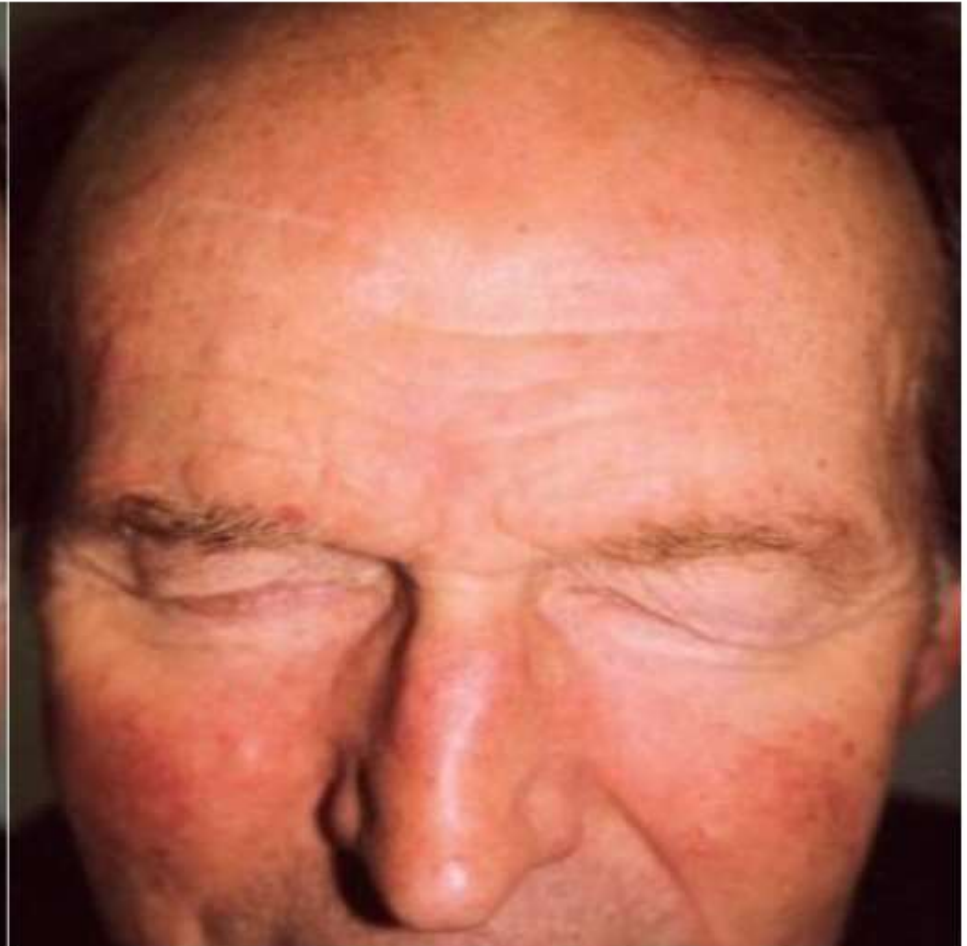




# GLG Pharma: Pipeline

Actinic keratosis Squamous cancer Treatment

7 day follow-up visit





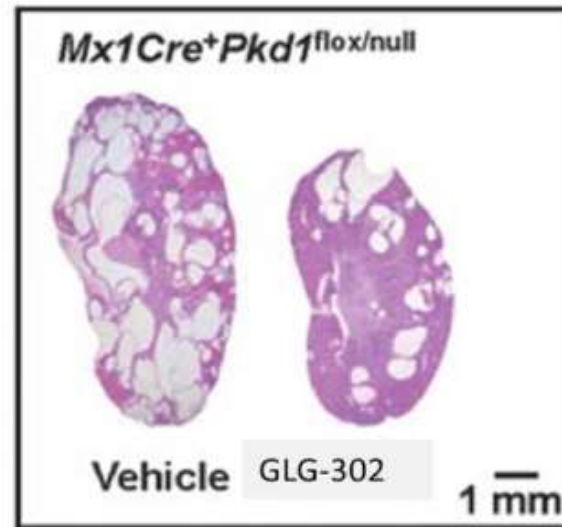
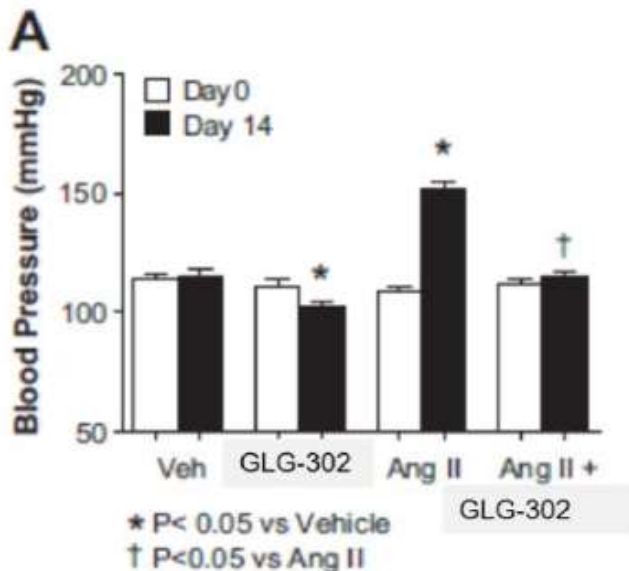
# GLG Pharma: Pipeline

- Kidney disease

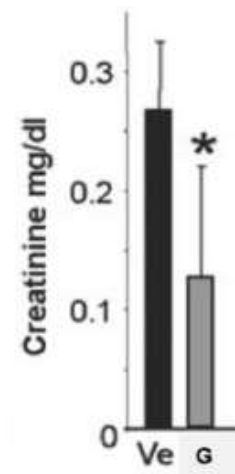
## Polycystic Kidney disease

GLG-302 demonstrated efficacy in animal models of ADPKD

- It showed: decreased kidney size, number of cysts and normalized kidney function.



Normal = 0.1 – 0.2 mg/dl



Mouse Polycystic Kidney treated with vehicle or GLG-302



# GLG Pharma: Pipeline

<b>Application/Publication Patent Number</b>	<b>Application/ Publication/ Issued Date</b>	<b>STATUS</b>	<b>Title</b>
US 2007/0191490 A1 11/701,722	Feb. 2007	Filed	Withacnistin Compounds for the Treatment of Cancer <b>GLG-101</b>
WO 2008/070697 A2 12/517,453	Jun. 2008	Filed	STAT3 Inhibitor Having Anti-Cancer Activity and Associated Methods - <b>GLG-202</b>
<b>European Patent No. 2120958</b>	Mar. 2013	Issued	
<b>Patent No. 7,960,434</b>	Jun. 2011	Issued	Small Molecule Inhibitors of STAT3 with Anti-tumor – <b>GLG-302 and analogs</b>
61/551,737	Oct. 2011	Filed	A Novel Platinum Compound That Inhibits Constitutive STAT3 Signaling and Induces Cell Cycle Arrest and Apoptosis of Malignant Cells – <b>GLG-401</b>
<b>Patent No. 8,445,517</b>	Mar. 2013	Issued	STAT Modulators - <b>GLG-801 and others</b>
61/533,379	Sept. 2011	Filed	Method and Compositions for Reducing Ischemic Stroke-Induced Damage to Neural Cells - <b>GLG-302</b>
<b>Patent No. 8,133,692</b>	Mar. 2012	Issued	Methods of predicting responsiveness to chemotherapeutic agents and selecting treatments - <b>Diagnostic</b>

## **CURRENT CORPORATE (see disclaimer) REVENUE PROJECTIONS**

- GLG-801 + Diagnostic for CLL and ADPKD - \$728MM 3-5 years
- GLG-302 + Diagnostic for CLL and ADPKD - \$4.5 BB 4-8 Years



# Leading causes of death

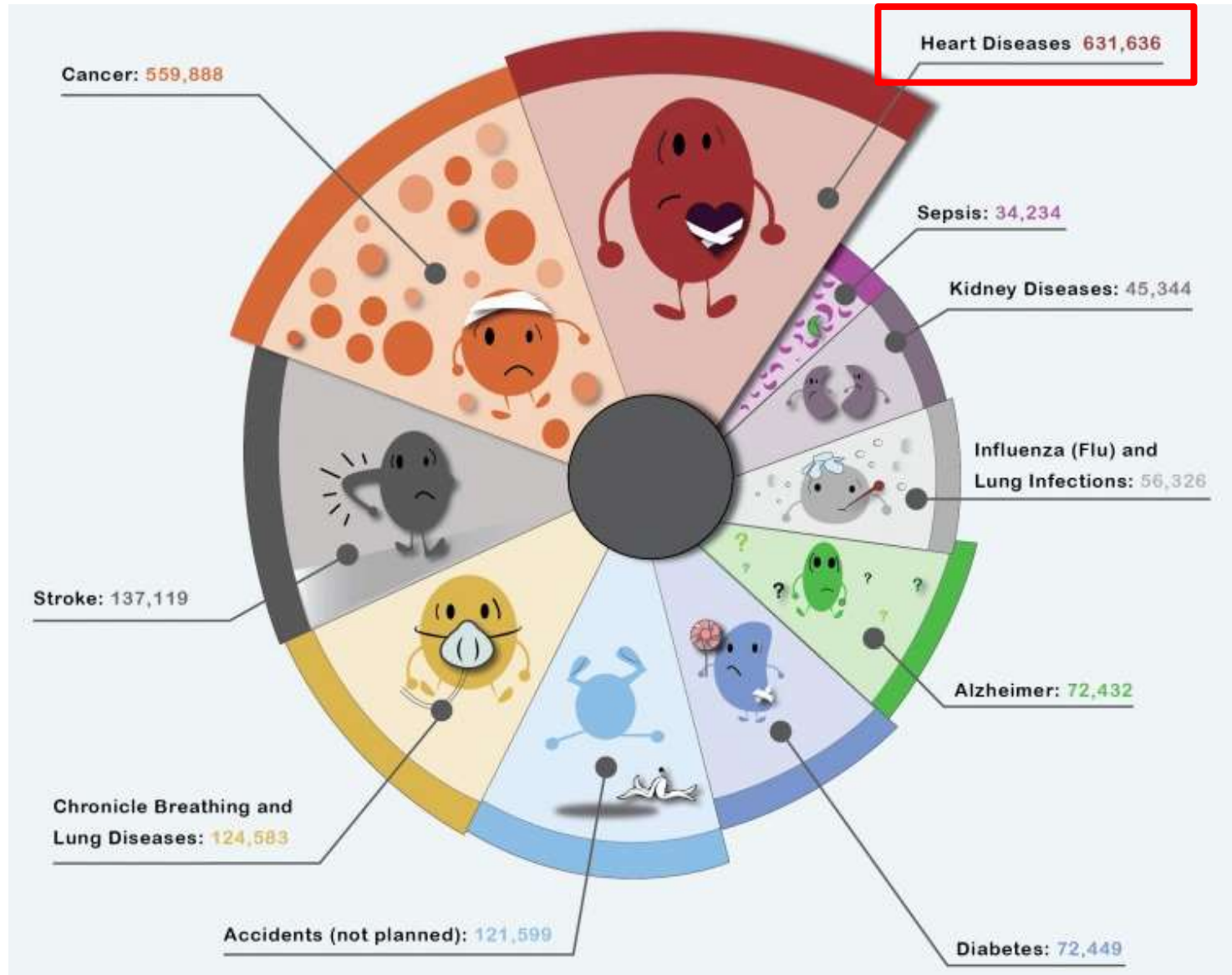
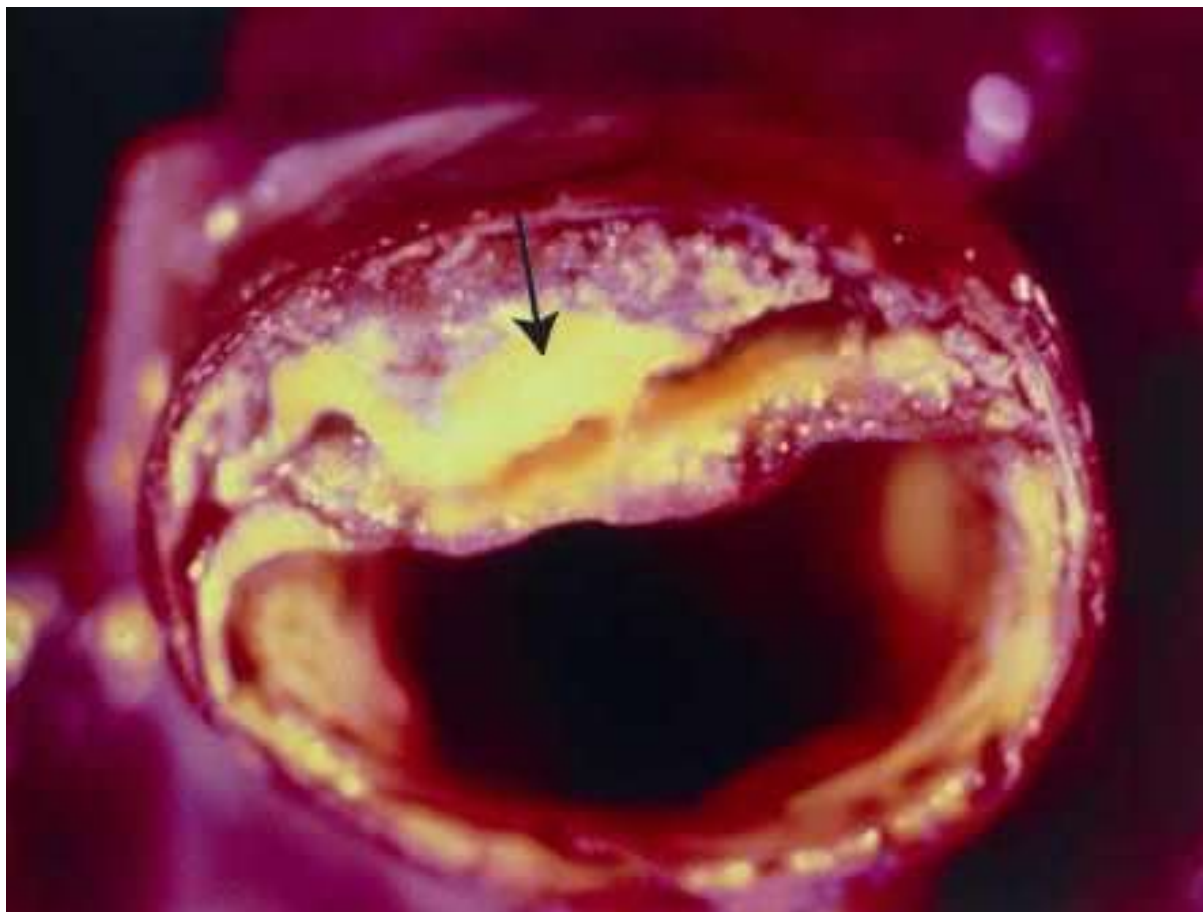


Fig. Top 10 causes of death in the USA. Centers for Disease Control and Prevention, 2016.

# Atherosclerosis

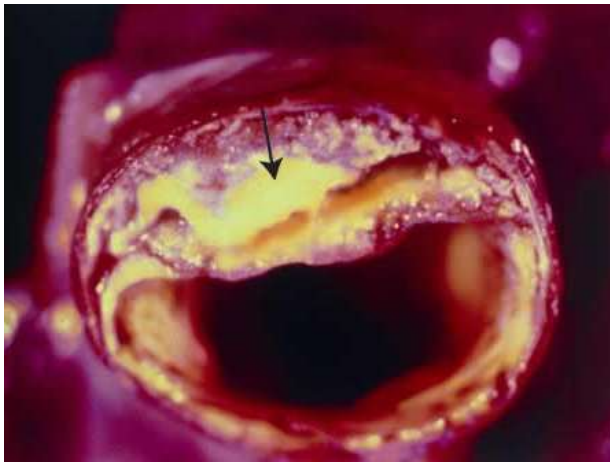
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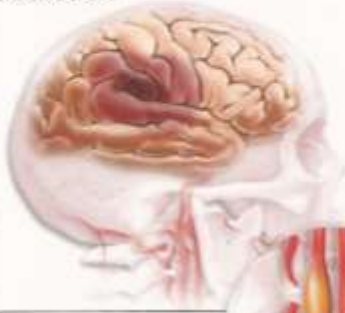
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Fig. Atherosclerotic plaque. BSIP VEM/Science photo library.

# Atherosclerosis



Ischemia and cerebral infarction



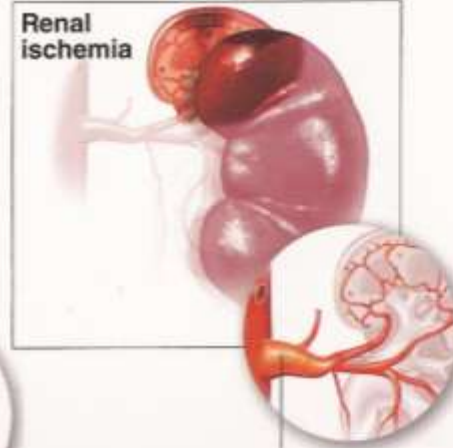
Internal carotid artery

Myocardial infarction



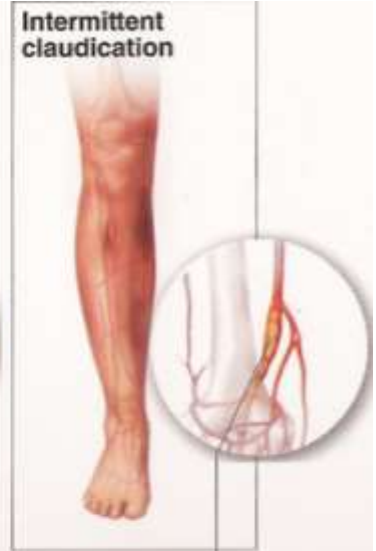
Coronary artery

Renal ischemia



Renal artery

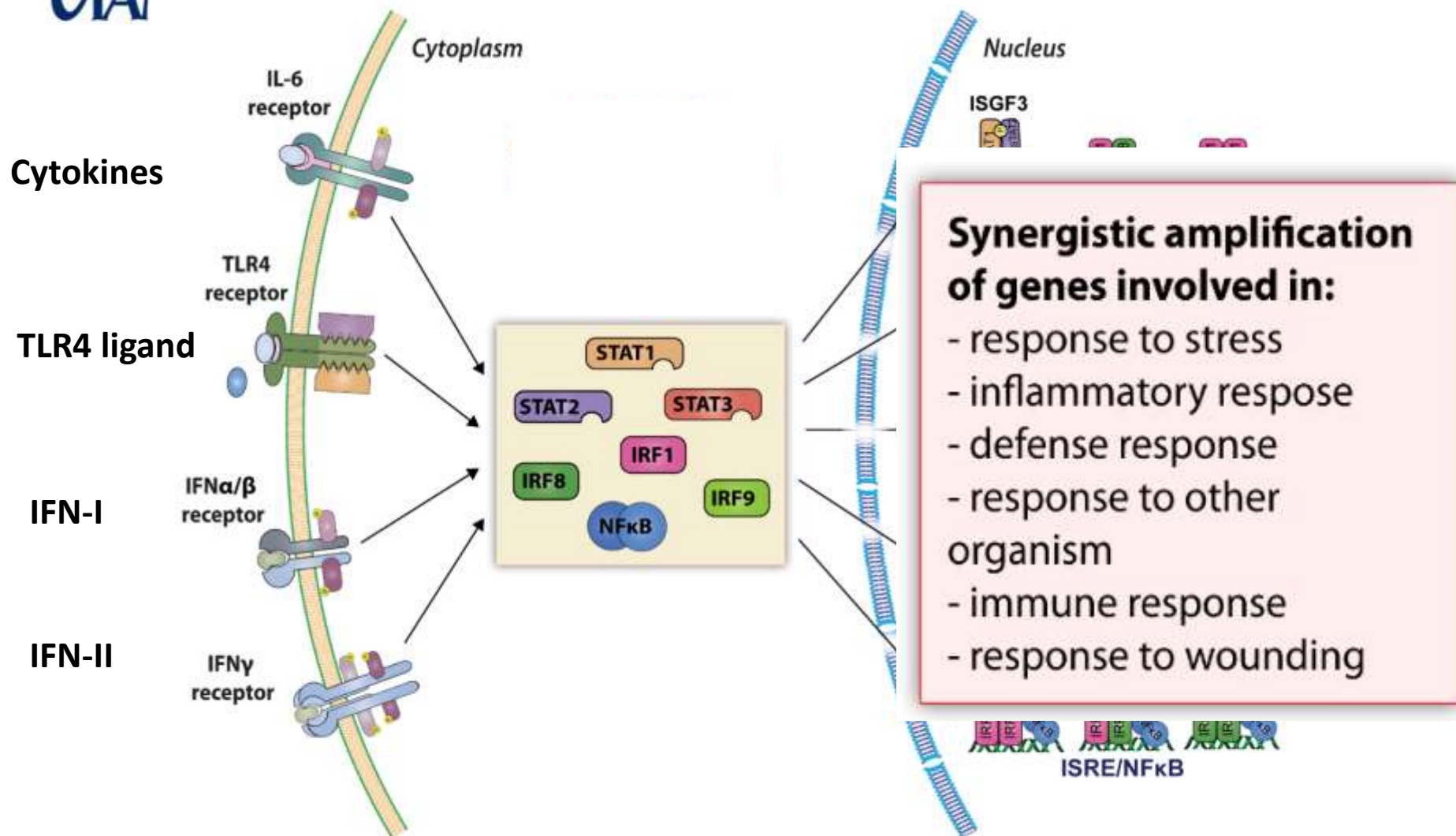
Intermittent claudication



Femoral artery

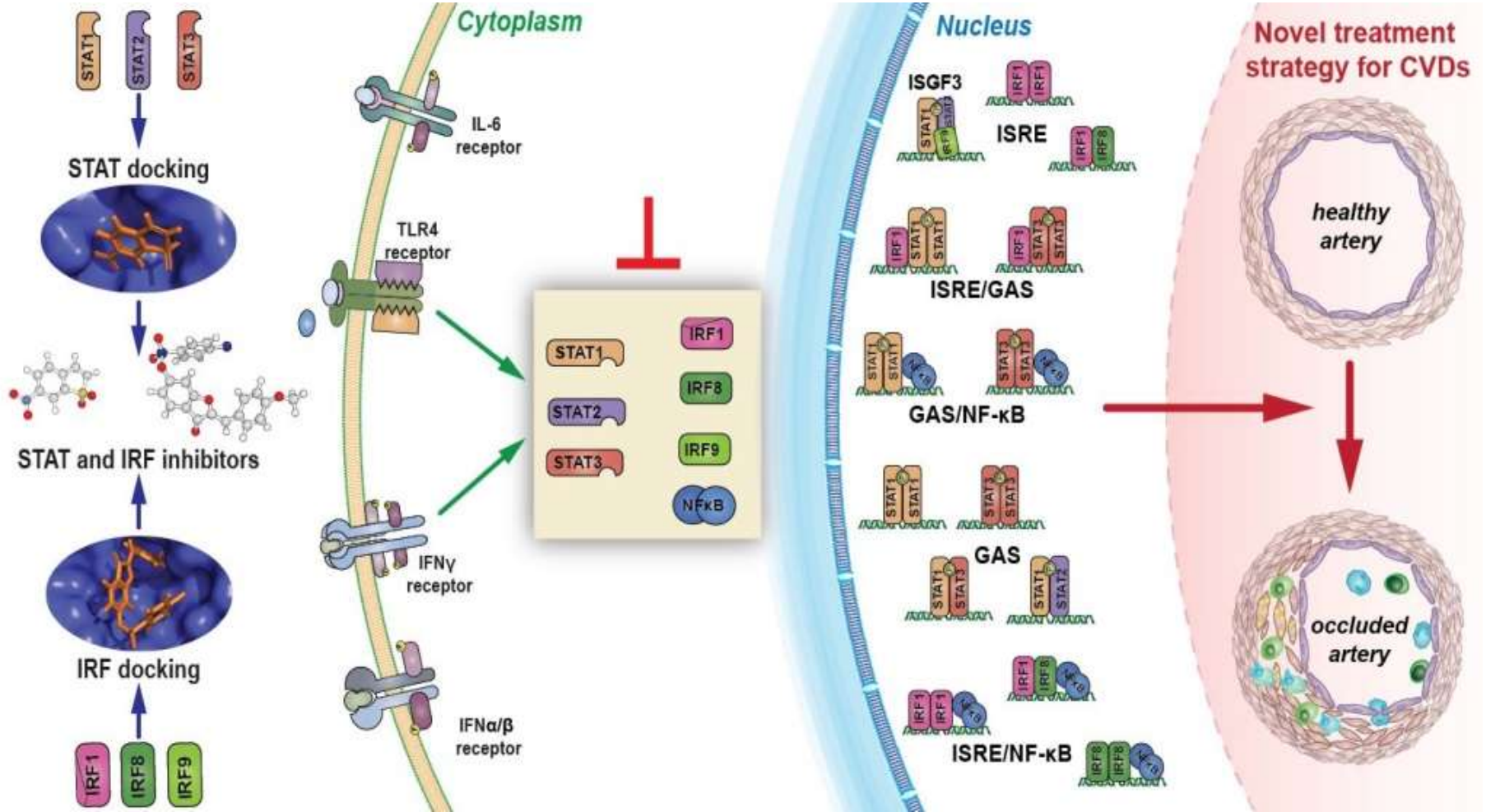
Fig. Atherosclerosis complications. Dr Philip Barlow Mills FCP (SA).

# STATs: Point of Conversion in Vascular Inflammation





# STAT inhibition approach LHMG



# STAT inhibition approach LHMG

