# Overview of drug targets for fibrosis

Rick Neubig, MD, PhD
Professor and Chair
Department of Pharmacology & Toxicology
Michigan State University
East Lansing, MI, USA

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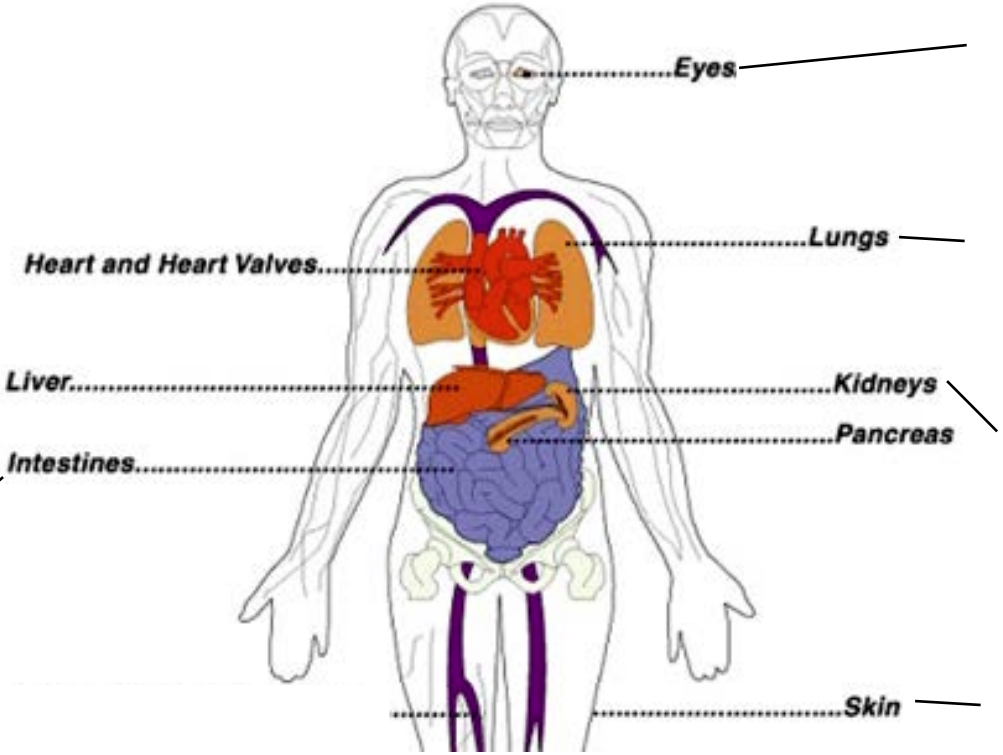
# Disclosures

- I am Founder and President of FibrosIX Inc. which has an SBIR grant to develop the CCG-203971 family of compounds an option to license them from The University of Michigan and Michigan State University.

# Diseases of fibrosis affect many organs




Glaucoma
Diabetic retinopathy
Dry eye

Idiopathic pulmonary fibrosis
Scleroderma lung disease
COPD

Transplant nephropathy
Diabetic nephropathy
FSGS

Hypertrophic scarring
Keloids

Myocardial infarction
Congestive heart failure

Hepatitis C
Alcoholic cirrhosis
NASH

Crohn's disease
Ulcerative colitis

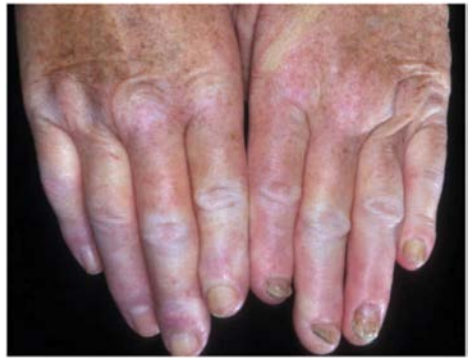
**Systemic fibrotic diseases**

Scleroderma/Systemic Sclerosis
Nephrogenic systemic fibrosis
Cystic fibrosis
Chronic Graft vs. Host Disease

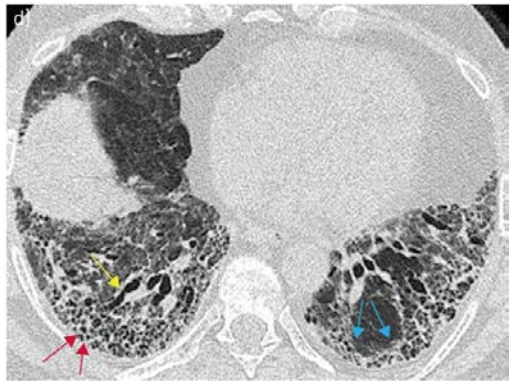
**Injury-associated fibrosis**

Post-surgical fibrosis
Burn-induced scarring and contractures
Radiation-induced fibrosis

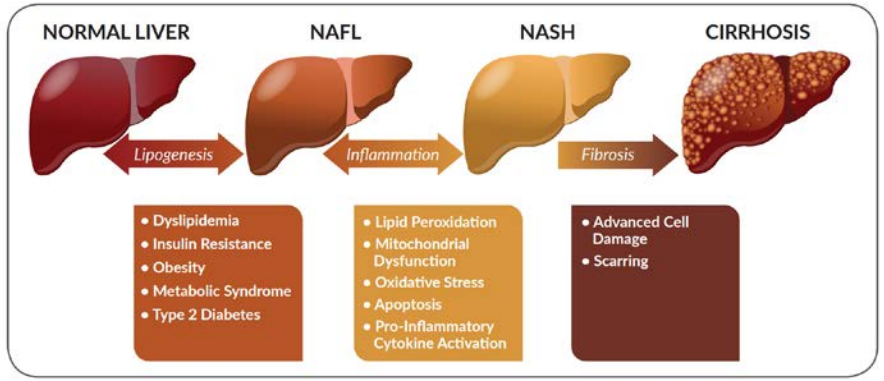
- **Scleroderma or Systemic sclerosis (SSc)**
  - Rare autoimmune disease of the skin - 4:1 females
  - Despite high morbidity and mortality
  - NO effective therapeutics exists



- **Idiopathic Pulmonary Fibrosis (IPF)**
  - Mortality
    - 50% at 2 years
    - 80% at 5 years

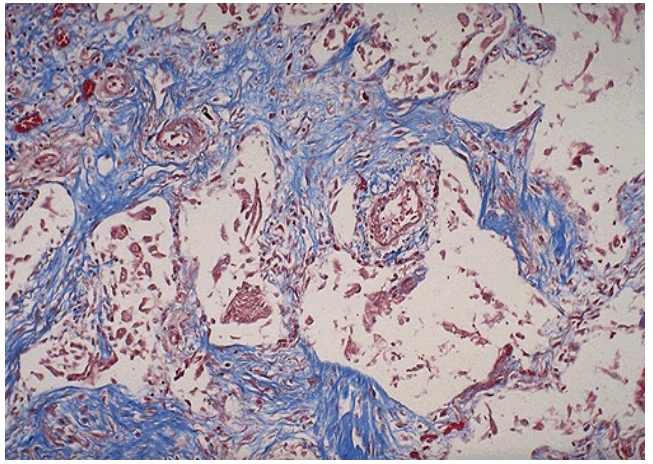


- **Non-alcoholic steatohepatitis (NASH) and Cirrhosis**
  - Common
    - 30-40 percent of adults in the United States have NAFLD. About **3 to 12 percent of adults in the United States have NASH**.
    - Patients with NASH and bridging fibrosis have **20% chance of progressing to cirrhosis.**



# Myofibroblast activation in fibrosis

- Fibrotic diseases have excess tissue collagen
- Organ failure results from normally flexible tissue hardened by extra-cellular matrix deposition

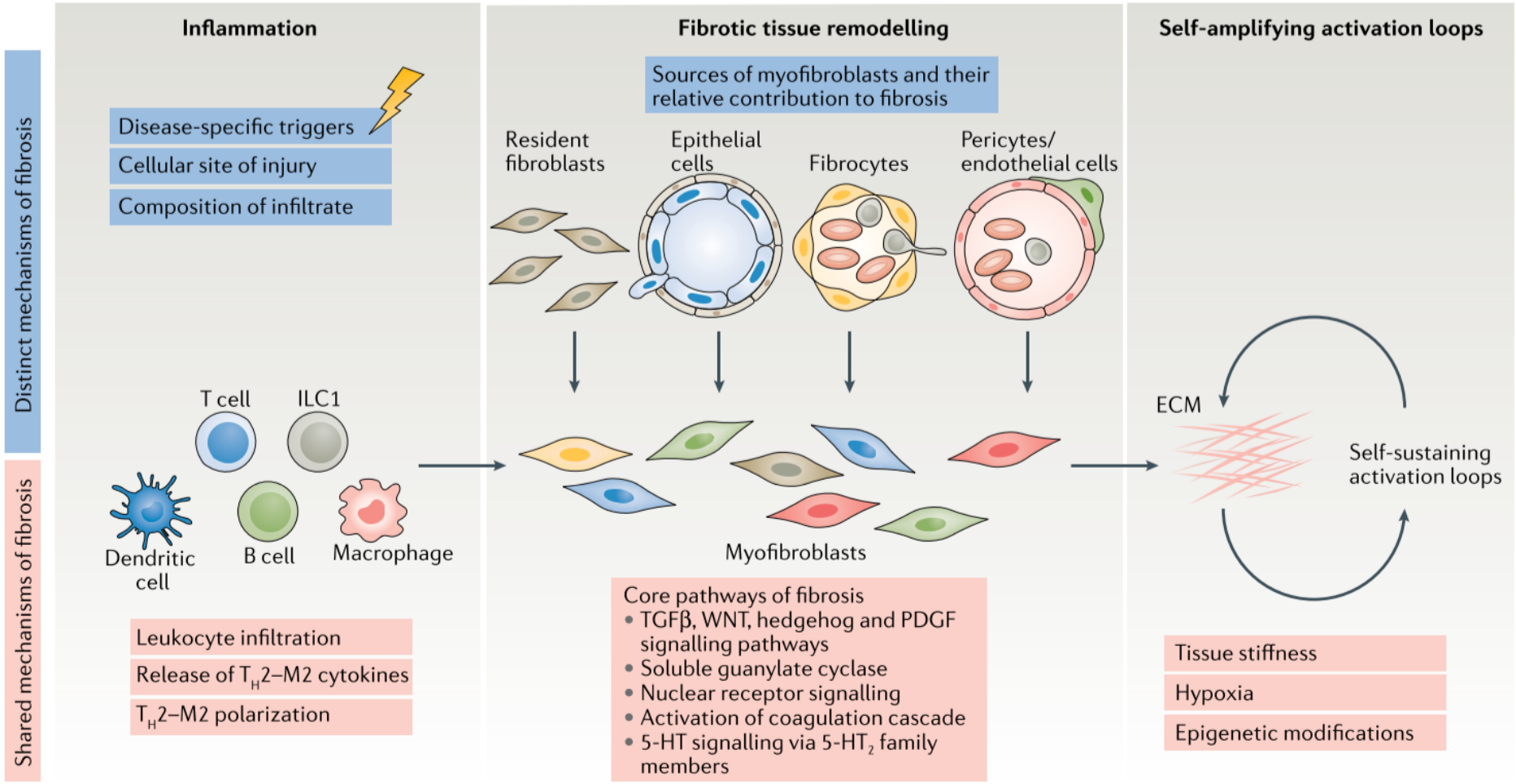


At the cellular level fibrosis is caused in part by stimulation of tissue fibroblasts, differentiating them into activated ***myofibroblasts***

Targeting core mechanisms leading to fibrosis represents a broad approach to therapy of many conditions in which fibrosis plays a role

http://library.med.utah.edu/WebPath/jpeg1/LUNG028.jpg

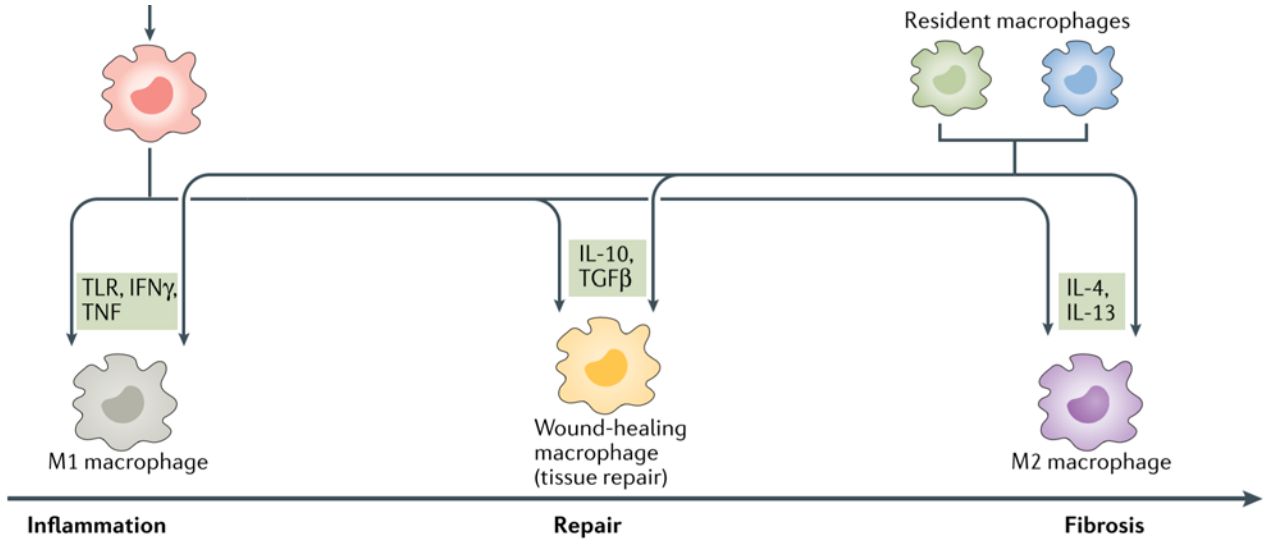
# Common and distinct mechanisms of fibrosis



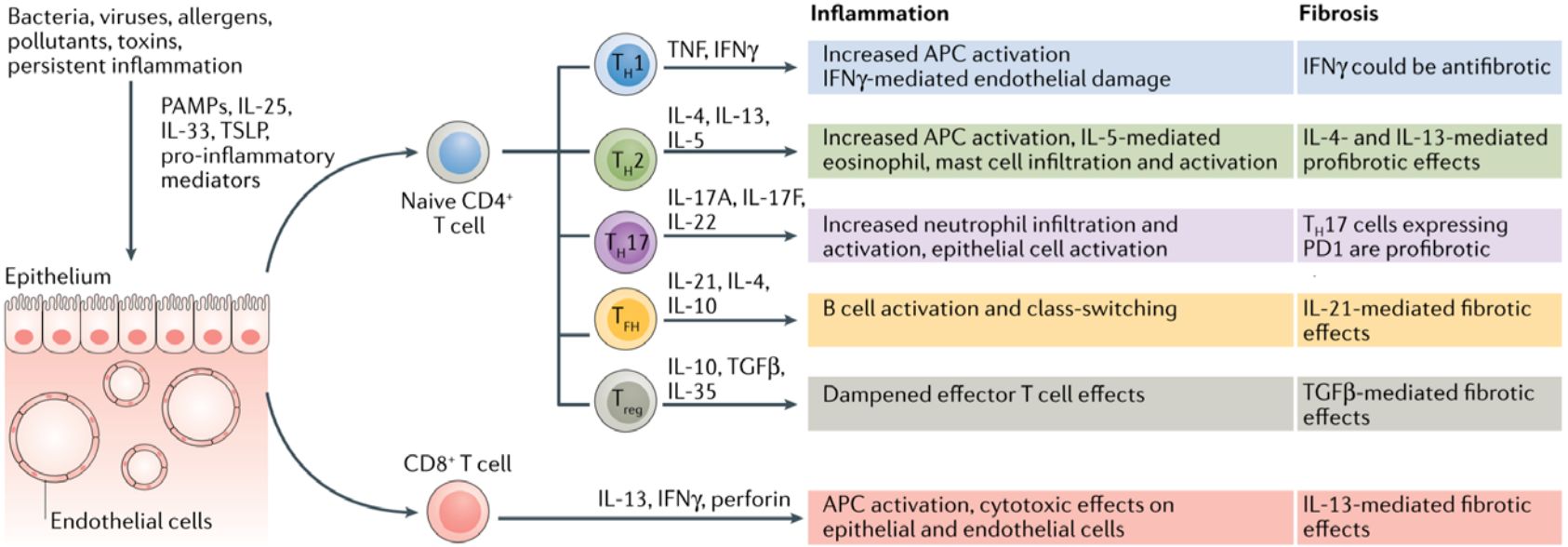

Distler et al, Nature Reviews Rheumatology 15: 705-730, 2019

# Cellular components of fibrosis

## Macrophages

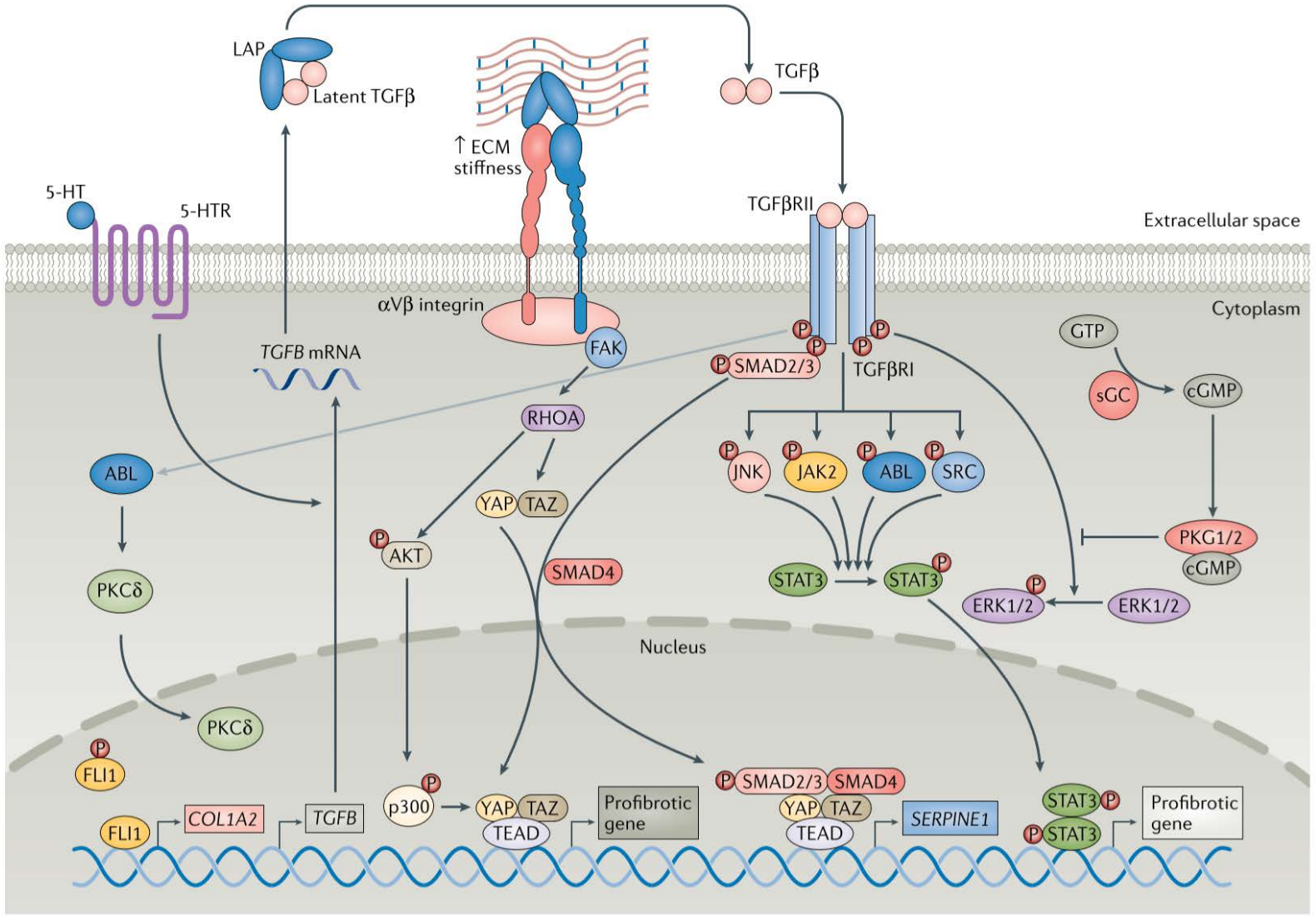



## T cells




Distler et al, Nature Reviews Rheumatology 15: 705-730, 2019

# Signaling pathways in fibrosis




Distler et al, Nature Reviews Rheumatology 15: 705-730, 2019

# Clinical trials in systemic sclerosis (SSc)

Table 4 | **Clinical trials in patients with SSc and IPF**

| Drug | Target | Target population | Phase | Clinical trial identifier | Status |
|---|---|---|---|---|---|
| *Systemic sclerosis* | | | | | |
| GLPG1690 | Autotaxin | SSc | II | NCT03798366 | Recruiting |
| IVIG | Fc receptors? | dcSSc | II | NCT01785056 | Active, not recruiting |
| Nintedanib | Multiple tyrosine kinases | SSc-associated ILD | III | NCT03313180 | Active, recruiting |
| Pirfenidone | Not well defined, but including TGFβ signalling | SSc-associated ILD | II | NCT03221257 | Recruiting |
| Tofacitinib | JAK1/3 | Early dcSSc | I/II | NCT03274076 | Active, not recruiting |
| GSK2330811 | Oncostatin | dcSSc | I/II | NCT03041025 | Recruiting |
| AVID200 | TGFβ1/TGFβ3 | dcSSc | I | NCT03831438 | Recruiting |
| Abatacept | CTLA4 | dcSSc | II | NCT02161406 | Completed |
| Tocilizumab | IL-6 | dcSSc | III | NCT02453256 | Completed |
| Riociguat | Soluble guanylate cyclase agonist | dcSSc | II | NCT02283762 | Completed |
| Brentuximab vedotin | CD30 | dcSSc | I/II | NCT03222492 | Recruiting |
| Romilkimab (SAR 156597) | IL-4 and IL-13 | dcSSc | II | NCT02921971 | Completed |
| Lenabasum (JBT-101) | CB2 agonist | dcSSc | III | NCT03398837 | Active, recruiting |
| Lanifibranor (IVA337) | PPARs | Early dcSSc | II | NCT02503644 | completed |

Approved Sept 2019

Failed*

Failed

**Failed 1 skin° endpoint 2° FVC endpoint improved*

Distler et al, Nature Reviews Rheumatology 15: 705-730, 2019

# Clinical trials in IPF

| *Idiopathic pulmonary fibrosis* | | | | | |
|---|---|---|---|---|---|
| Pirfenidone | Not well defined, but including TGFβ signalling | Pulmonary fibrosis with anti-myeloperoxydase antibodies | II | NCT03385668 | Recruiting |
| Bevasizumab | VEGF | Radiation-/ chemotherapy-induced pulmonary fibrosis | II | NCT01917877 | Recruiting |
| TRK-250 | RNA-based inhibition of TGFβ1 expression | IPF | I | NCT03727802 | Recruiting |
| FG-3019 | CTGF | IPF | II | NCT01262001 | Completed |
| VAY736 | BAFFR | IPF | II | NCT03287414 | Recruiting |
| GLPG1205 | GPR84 | IPF | II | NCT03725852 | Recruiting |
| ND-L02-s0201 | HSP47 (collagen-specific chaperone) | IPF | II | NCT03538301 | Recruiting |
| BG00011 | αVβ6 integrin | IPF | II | NCT03573505 | Active, not recruiting |
| CC-90001 | JNK1 | IPF | II | NCT03142191 | Recruiting |
| GLPG1690 | Autotaxin | IPF | III | NCT03711162 | Recruiting |
| Elafibranor | PPARα/δ | Nonalcoholic steatohepatitis with fibrosis | III | NCT02704403 | Recruiting |

Unknown

Distler et al, Nature Reviews Rheumatology 15: 705-730, 2019

# IPF, Cirrhosis, and SSc Trials (Nov 2020) extracted from clinicaltrials.gov

| | |
|---|---|
| • **Total trials** | **1327** |
| • **Total Therapeutic** | **619** |
| • Pulmonary Fibrosis | 221 |
| • Cirrhosis | 161 |
| • Sclero(derma/sis) | 211 |
| • Raynauds | 32 |

Extracted from Clinical Trials.gov Nov 2020
R. Neubig, unpublished

# Fibrosis trials drug classes

| | | |
|---|---|---|
| 1 | GPCR | 93 |
| 2 | Cell Rx | 68 |
| 3 | Antibody | 54 |
| 4 | Enzyme | 48 |
| 5 | KI | 48 |
| 6 | Immunosupp | 36 |
| 7 | Biologic | 29 |
| 8 | Unknown | 26 |
| 9 | NR | 21 |
| 10 | Imaging | 14 |
| 11 | Antibiotic | 13 |
| 12 | Gas | 13 |
| 13 | Cytokine | 12 |
| 14 | Interferon | 11 |
| 15 | Antiviral | 10 |
| 16 | Channel | 10 |
| 17 | Antioxidant | 9 |
| 18 | Dx | 9 |
| 19 | Integrin | 7 |
| 20 | Metabolite | 6 |
| 21 | NP | 6 |
| 22 | ECM | 5 |
| 23 | Immunomodulator | 5 |
| 24 | Protease Inhibitor | 5 |
| 25 | Proton Pump Inh | 5 |
| 26 | Anticoagulant | 4 |
| 27 | Combination | 4 |
| 28 | Nucleic Acid | 4 |
| 29 | Osmotic/Oncotic | 3 |
| 30 | Probiotic | 3 |
| 31 | Anesthetic | 2 |
| 32 | Anti-sickle | 2 |
| 33 | Antiparastic | 2 |
| 34 | Chelator | 2 |
| 35 | Hormone | 2 |
| 36 | Light | 2 |
| 37 | Muscle relaxant | 2 |
| 38 | Tubulin Inhibitor | 2 |
| 39 | Wnt inhibitor | 2 |
| 40 | ADC | 2 |
| 44 | Antithrombotic | 2 |
| 45 | Antidiabetic | 1 |
| 46 | Bile acid | 1 |
| 47 | Biomarker | 1 |
| 48 | Bisphophonate | 1 |
| 49 | Cytokine/Hormone | 1 |
| 50 | Ion channels | 1 |
| 51 | Mast cell stabilizer | 1 |
| 52 | Metal | 1 |
| 53 | Multiple | 1 |
| 54 | Natriuretic peptide | 1 |
| 55 | NR/GPCR | 1 |
| 56 | Nucleic Acid | 1 |
| 57 | Peptide | 1 |
| 58 | Physical agent | 1 |
| 59 | PPI | 1 |
| 60 | Protease inhibitor | 1 |
| 61 | Stem cell mobilizer | 1 |
| 62 | Sugar | 1 |
| 63 | TF | 1 |
| 64 | Unknown/KI | 1 |

Extracted from Clinical Trials.gov Nov 2020
R. Neubig, unpublished

# Fibrosis trials drug targets_agents

| | | | |
|---|---|---|---|
| 1 | None | 76 | |
| 2 | ET | 34 | |
| 3 | MSC | 25 | |
| 4 | FGF VEGF PDGF | 18 | |
| 5 | pirfenidone | 17 | |
| 6 | PDE5 | 15 | |
| 7 | Cyclophosphamide | 11 | |
| 8 | IP receptor | 11 | |
| 9 | Abl Kit PDGF | 10 | |
| 10 | sGC | 8 | |
| 11 | SVF | 8 | |
| 12 | CD20 | 7 | |
| 13 | IFNg1b | 7 | |
| 14 | IL13 | 7 | |
| 15 | Microbiome | 7 | |
| 16 | Autotaxin | 6 | |
| 16 | alphav beta6 | 6 | |
| 17 | N-Ac-cysteine | 6 | |
| 18 | Botox | 5 | |
| 19 | Combination | 5 | |
| 20 | CTGF | 5 | |
| 21 | LPA1R antagonist | 5 | |
| 22 | Mycophenolate | 5 | |
| 23 | O2 | 5 | |
| 24 | beta adrenergic | 4 | |
| 25 | FXR | 4 | |
| 26 | GR | 4 | |
| 27 | HBV nucleoside | 4 | |
| 28 | IFNa | 4 | |
| 29 | IVIG | 4 | |
| 30 | JNK | 4 | |
| 31 | MOR | 4 | |
| 32 | Nucleotide | 4 | |
| 33 | Pentraxin | 4 | |
| 34 | Stem cell transplant | 4 | |
| 35 | Adipose | 3 | |
| 36 | G-CSF | 3 | |
| 37 | Methotrexate | 3 | |
| 38 | mToR | 3 | |
| 39 | NO | 3 | |
| 40 | Statin | 3 | |
| 41 | TGF-beta antagonist | 3 | |
| 42 | Thalidomide | 3 | |
| 43 | V2R | 3 | |
| 44 | Albumin | 2 | |
| 47 | Aminoacids | 2 | |
| 49 | AT1R | 2 | |
| 50 | AT2R | 2 | |
| 51 | BLyS | 2 | |
| 52 | Bone marrow | 2 | |
| 53 | CB2 | 2 | |
| 54 | Collagen | 2 | |
| 55 | CTLA-4 | 2 | |
| 56 | ET/PDE5 | 2 | |
| 57 | FGF21 | 2 | |
| 58 | Fuzhenghuayu | 2 | |
| 59 | Galectin-3 | 2 | |
| 60 | HCV Protease Inhibitor | 2 | |
| 61 | HSC | 2 | |
| 62 | HSP47 siRNA | 2 | |
| 63 | IL17R | 2 | |
| 64 | IL4 IL13 | 2 | |
| 65 | LOXL2 | 2 | |
| 66 | Lung stem cells | 2 | |
| 67 | Nintedanib | 2 | |
| 68 | NO | 2 | |
| 69 | Nrf2 | 2 | |
| 70 | O3 | 2 | |
| 71 | Oncostatin M (OSM) | 2 | |
| 72 | P2X3 inhibitor | 2 | |
| 73 | pan-caspase | 2 | |
| 74 | pomalidomide | 2 | |
| 75 | Probiotic | 2 | |
| 76 | Relaxin | 2 | |
| 77 | ROCK2 | 2 | |
| 78 | Thrombin | 2 | |
| 79 | Thymocytes | 2 | |
| 80 | TKI | 2 | |
| 81 | TLR8/9 | 2 | |
| 82 | Unknown | 2 | |
| 83 | VGCC | 2 | |
| 84 | Voxelotor | 2 | |
| 85 | Yirfenidone | 2 | |

+ 157 more singlets

Extracted from Clinical Trials.gov Nov 2020
R. Neubig, unpublished

# Fibrosis drugs by class

| GPCR | |
|---|---|
| 1 ET | 34 |
| 2 IP receptor | 19 |
| 3 LPA1R antagonist | 5 |
| 4 beta adrenergic | 4 |
| 5 MOR | 4 |
| 6 V2R | 3 |
| 7 AT1R | 2 |
| 8 AT2R | 2 |
| 9 CB2 | 2 |
| 10 Relaxin | 2 |

| Kinase Inhibitors | |
|---|---|
| 1 Nintedanib | 20 |
| 2 Imatinib | 9 |
| 3 CC-90001 | 3 |
| 4 KD025 | 2 |

| Enzymes | |
|---|---|
| 1 PDE5 | 15 |
| 2 sGC | 8 |
| 3 Autotaxin | 6 |
| 4 Statin | 3 |
| 5 Thrombin | 2 |

| Antibody Drugs | |
|---|---|
| 1 CD20 | 7 |
| 2 IL13 | 7 |
| 3 CTGF | 5 |
| 4 IVIG | 4 |
| 5 BLyS | 2 |
| 6 IL17R | 2 |
| 7 IL4 IL13 | 2 |
| 8 LOXL2 | 2 |
| 9 Oncostatin M (OSM) | 2 |

| Biologicals | |
|---|---|
| 1 Microbiome | 7 |
| 2 Botox | 5 |
| 3 Pentraxin | 4 |
| 4 CTLA-4 | 2 |
| 5 Probiotic | 2 |

| Immunosuppressants | |
|---|---|
| 1 Cyclophosphamide | 11 |
| 2 Mycophenolate | 5 |
| 3 Combination | 4 |
| 4 Nucleotide | 4 |
| 5 Methotrexate | 3 |
| 6 mToR | 3 |
| 7 TLR8/9 | 2 |

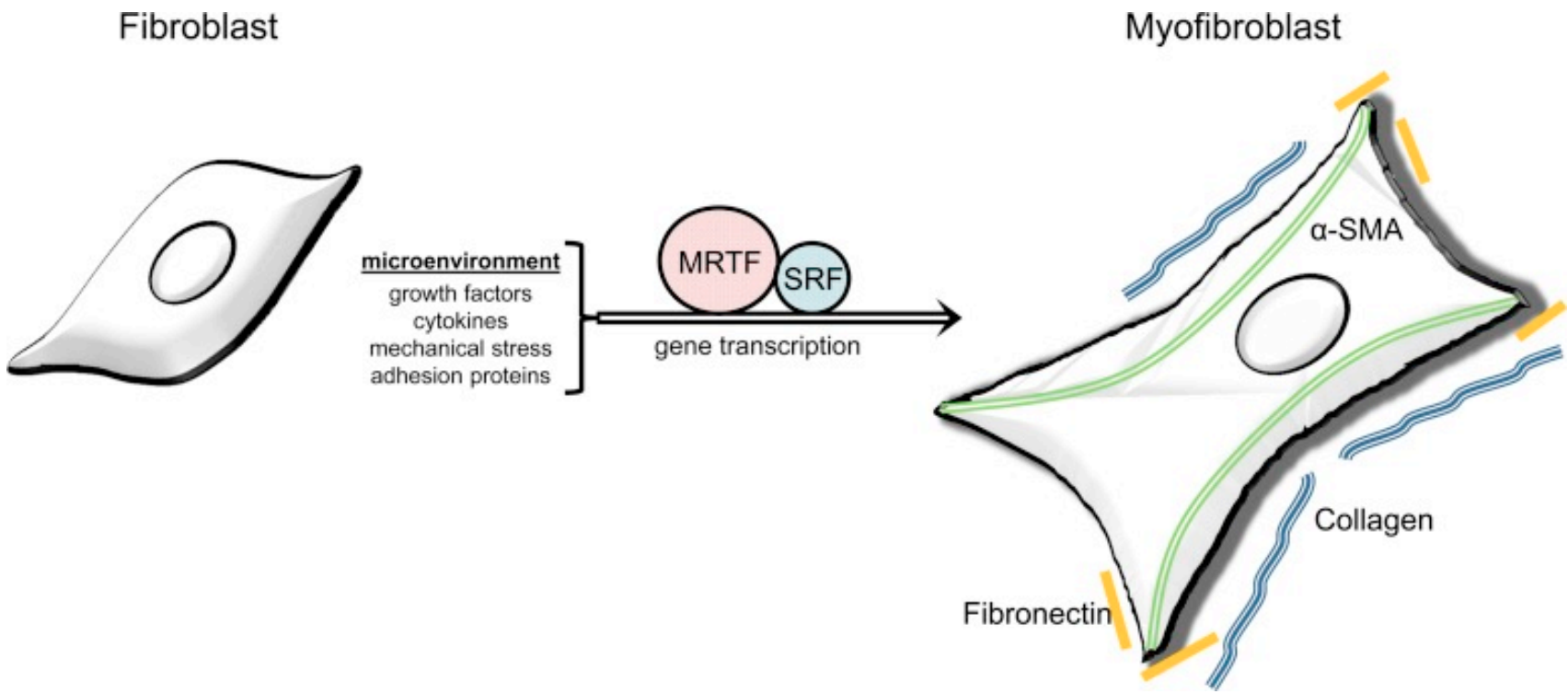
Extracted from Clinical Trials.gov Nov 2020
R. Neubig, unpublished

# Fibrosis trials Unknown mechanism/target

| Drug | n | Indication | Mechanism/Target? |
|---|---|---|---|
| Pirfenidone | 18 | IPF | affects TGF-beta |
| Bi 1015550 | 2 | IPF | |
| Hec585 | 2 | IPF | |
| Iguratimod | 1 | SSc | ↓ NFκB activity |
| Pbi4050 | 1 | IPF | |
| Td-1058 | 1 | IPF | |
| Zl-2102 | 1 | IPF | |
| Zsp1603 | 1 | IPF/Ca | PDGFR |

Extracted from Clinical Trials.gov Nov 2020
R. Neubig, unpublished

# Fibroblast to Myofibroblast Transition is a Hallmark of Fibrotic Diseases



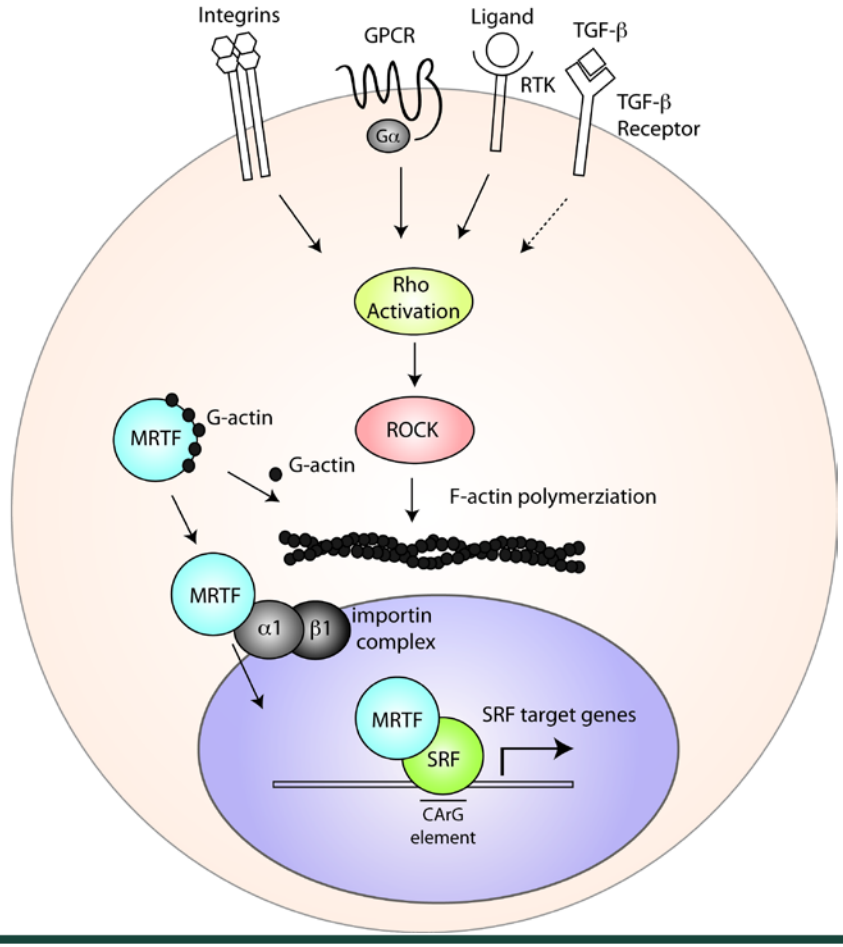

*Tsou et al, Am J Physiol Cell Physiol 2014*

# Myocardin Related Transcription Factor (MRTF): Serum Response Factor (SRF) Signaling and Rho

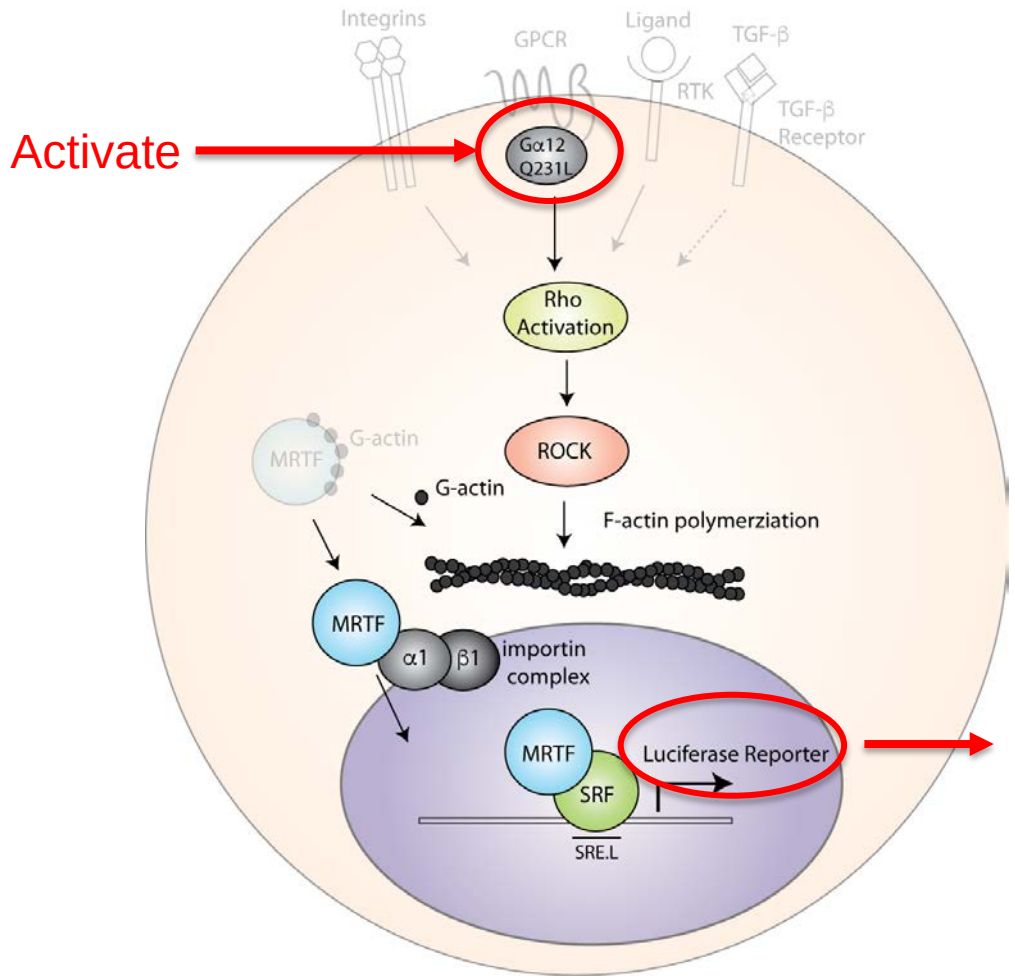
Rho is activated by many drivers of fibrosis

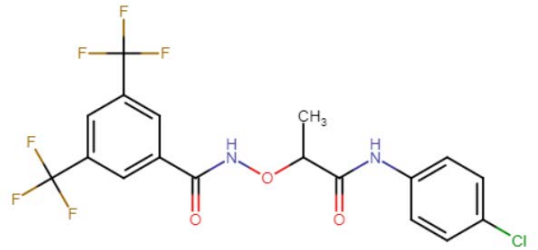
GPCRs – LPA, Endothelin
TGF-β receptor - TGF-β
RTKs – PDGF, VEGF
Integrins – CTGF

All can activate Rho-MTRF pathway

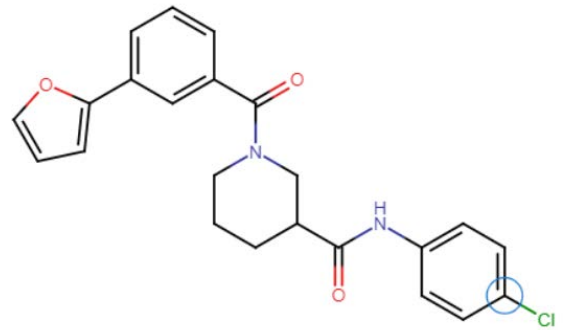


# SRE.L Luciferase Assay – pathway screen



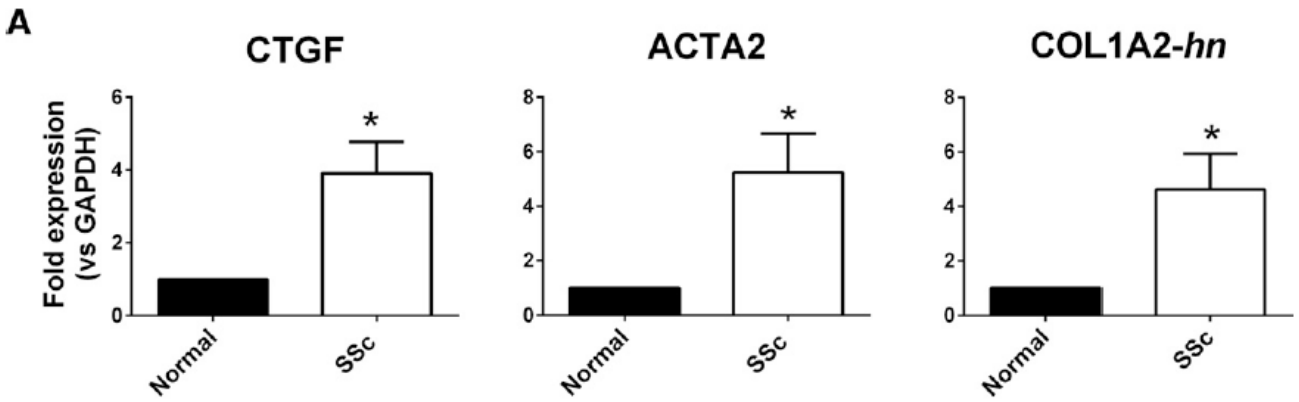
CCG-1423



CCG-203971

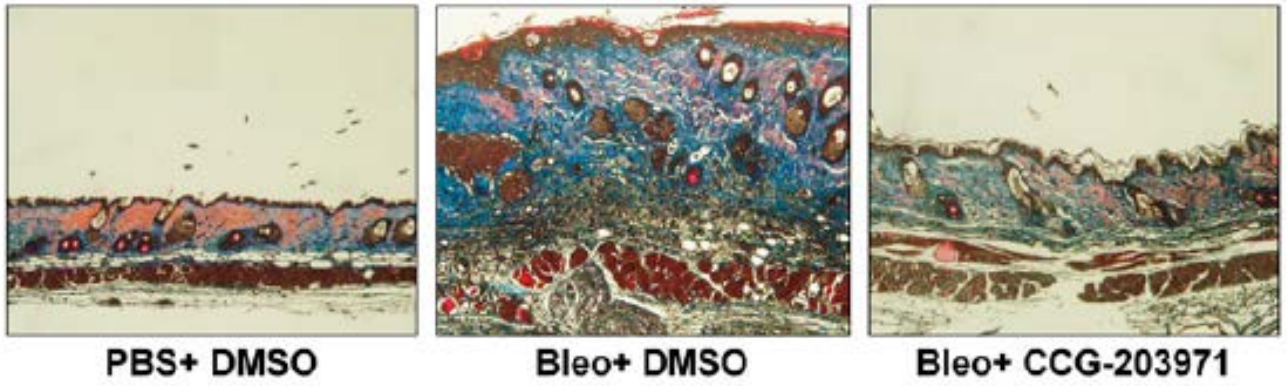
*Evelyn et al, Mol Canc Ther* 2007.

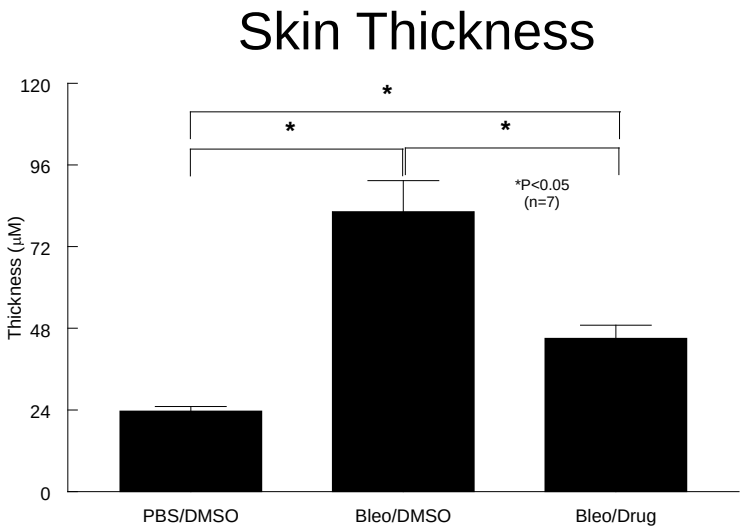
# MRTF-regulated gene expression increased in SSc
# CCG-203971 can reduce CTGF, ACTA2 and Col1A2 mRNA

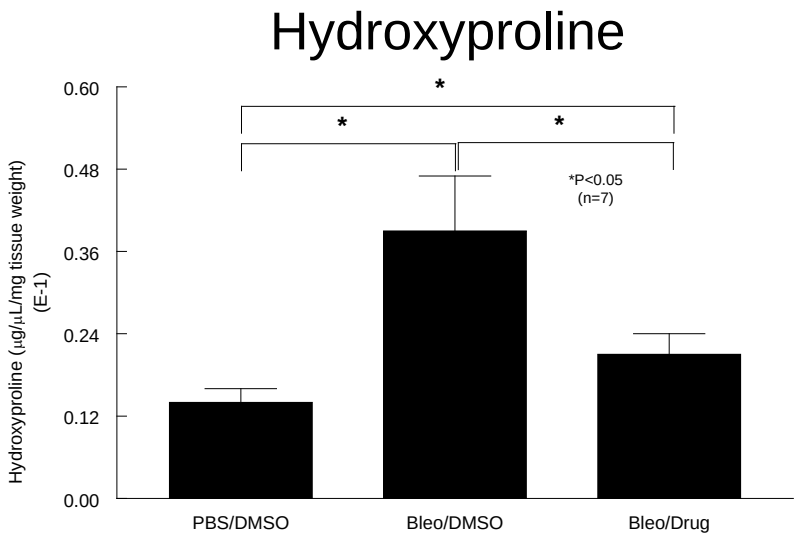



*Haak et al, JPET 2014*

# CCG-203971 prevents bleomycin induced skin fibrosis

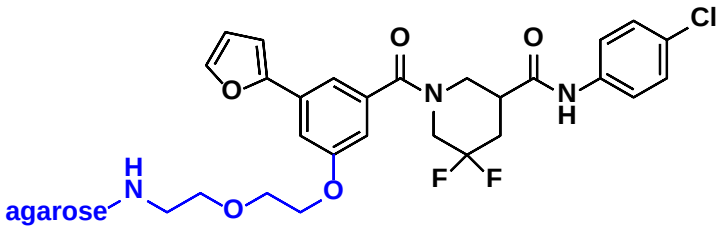


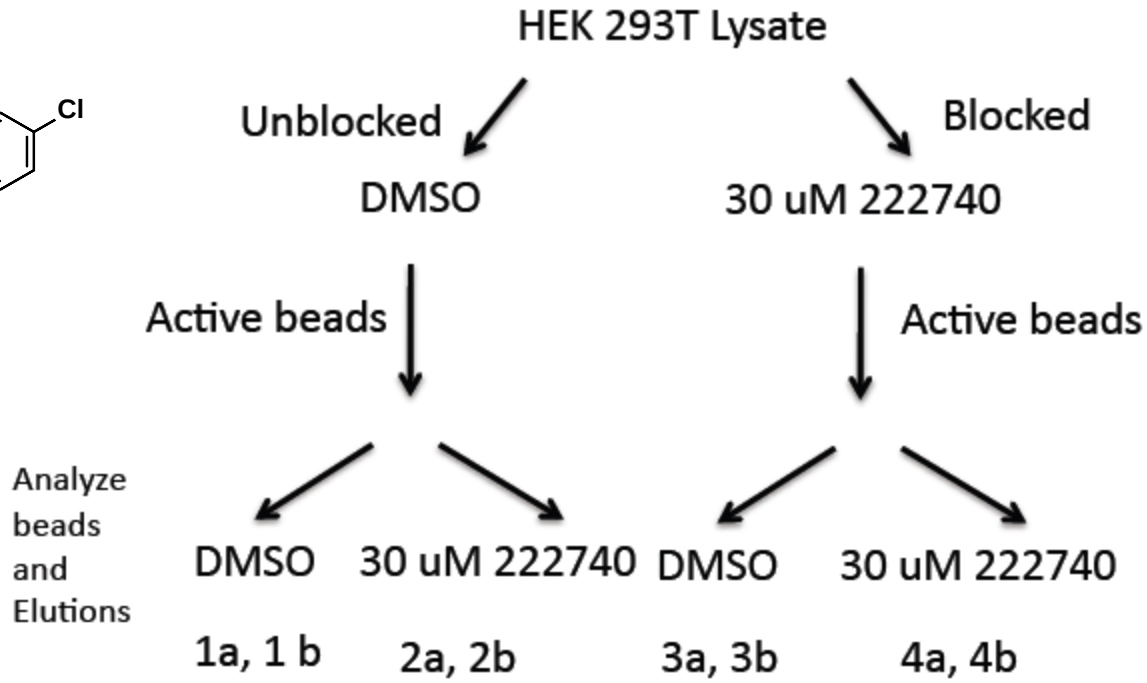




Haak et al JPET 349:480-6 , 2014

# Target ID - Unbiased Proteomic Approach



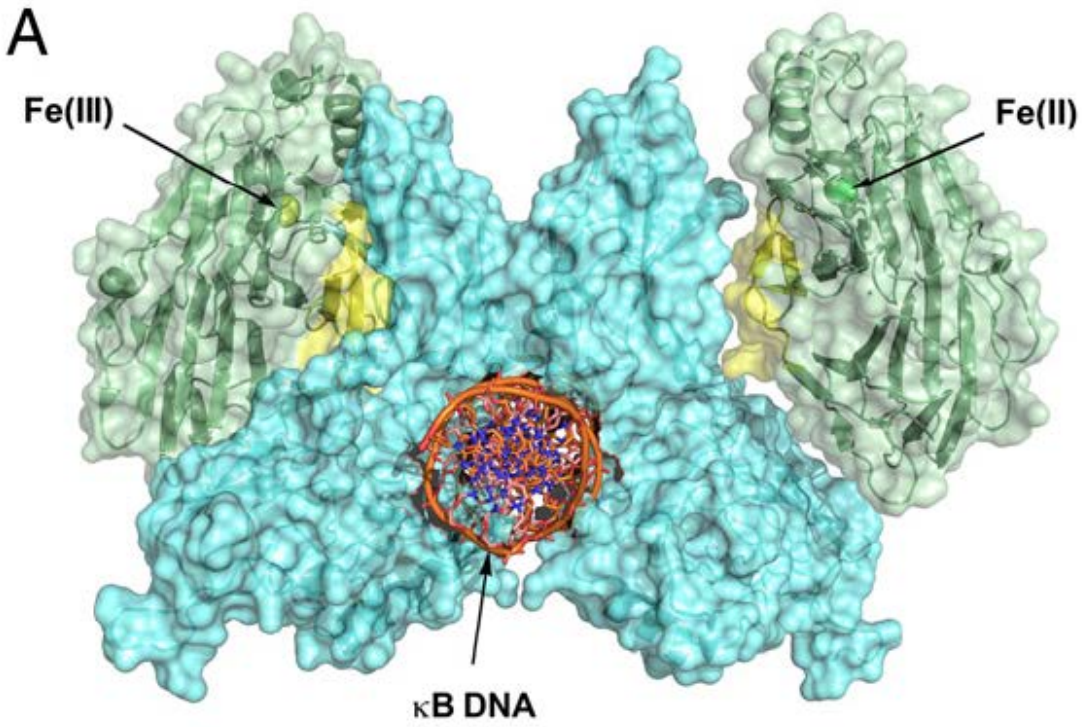




2 samples each
3 technical mass spec measurements

# Pirin

- Co-transcription factor thought to be redox dependent
- Enhances NF-κB binding to DNA

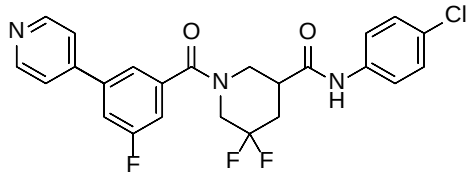
- Upregulated in melanoma
- Highly expressed in pDC cells which are implicated in SSc



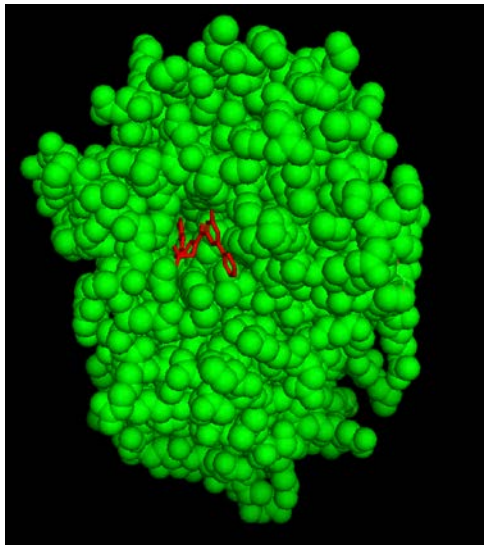

Model made using ZDOCK

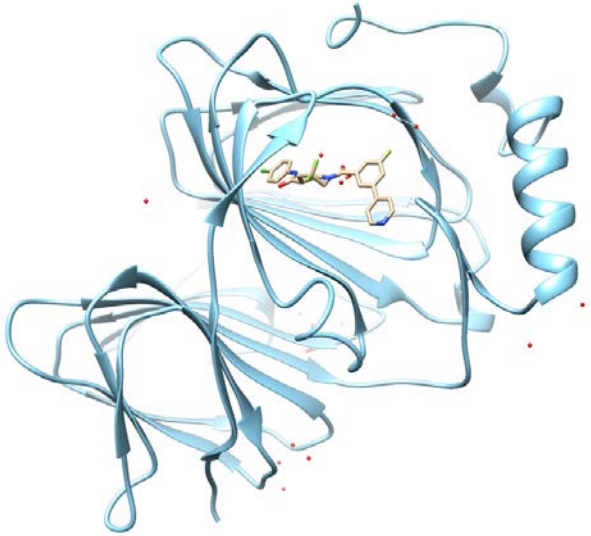
*Liu et al, PNAS 2013*

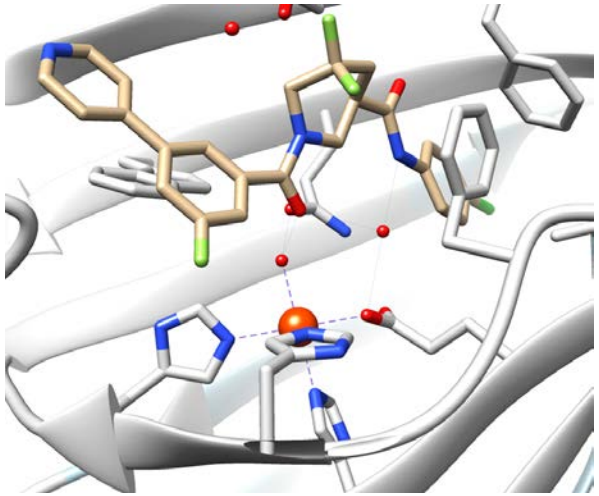
# Crystal Structure of CCG-257081 bound to Pirin




**CCG-257081**



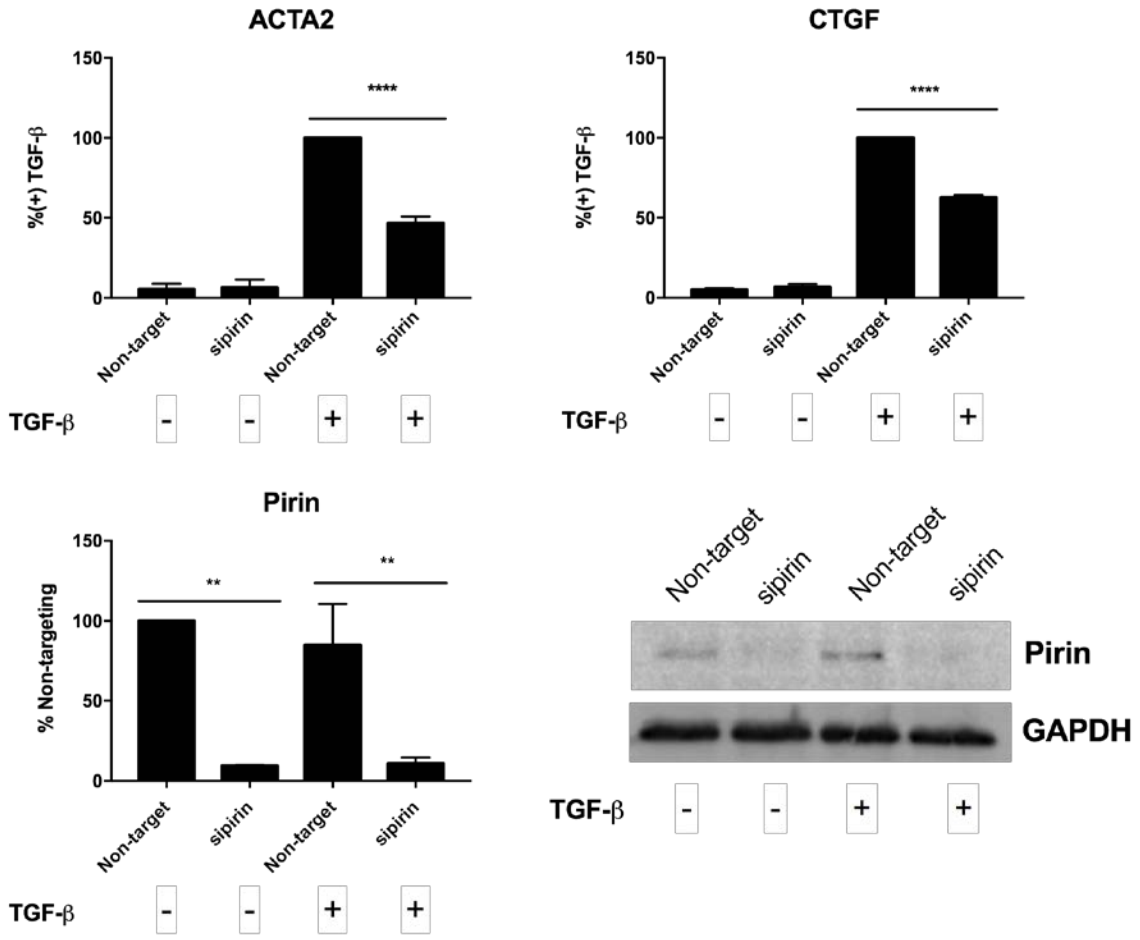




His-tagged full length recombinant pirin was purified from E.coli and crystallized using the hanging drop method in 0.1 M HEPES ph 7.5, 8% ethylene glycol and 20% PEG 8000. CCG-257081 was soaked into pre-formed crystals and data was collected at APC to 1.5 Å

Lisabeth et al ACS Pharm Trans Sci 2: 92–100 2019

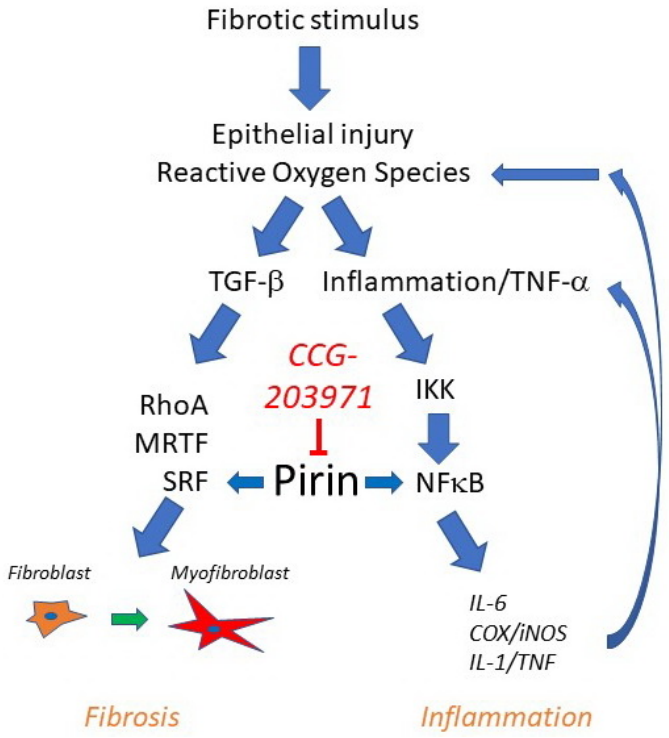
# Knockdown of Pirin reduces TGFβ induced ACTA2 and CTGF



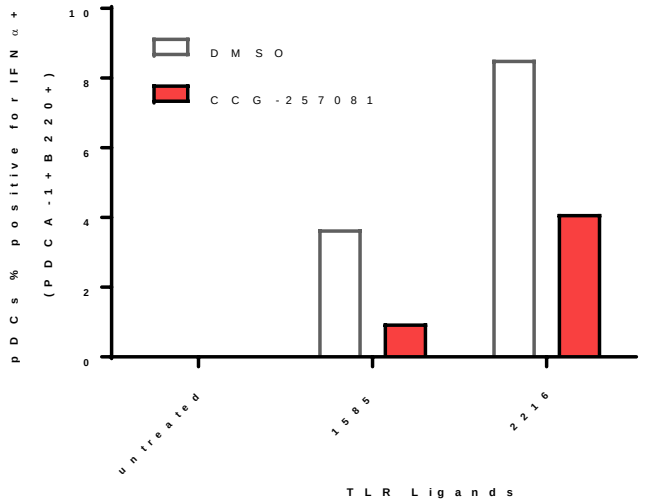

Lisabeth et al ACS Pharm Trans Sci 2: 92–100 2019

# Novel attributes of pirin-inhibitor CCG compounds in fibrosis and scleroderma

## Dual MRTF & NFκB inhibitor




## Suppression of Plasmacytoid dendritic cells - pDC



# Summary

- CCG series of compounds have been shown to be effective in melanoma and fibrotic disease models
- A molecular target, Pirin, identified through an unbiased proteomic approach
- CCG compounds bind to Pirin *in vitro* with excellent co-crystal
- **Pirin is a novel drug target for fibrosis and cancer with unique mechanisms identified by academic drug discovery/chemical biology work**
- Active development of the CCG compounds for clinical use is underway

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