



*pro-inflammatory marker (together with TNF and IL-1)*

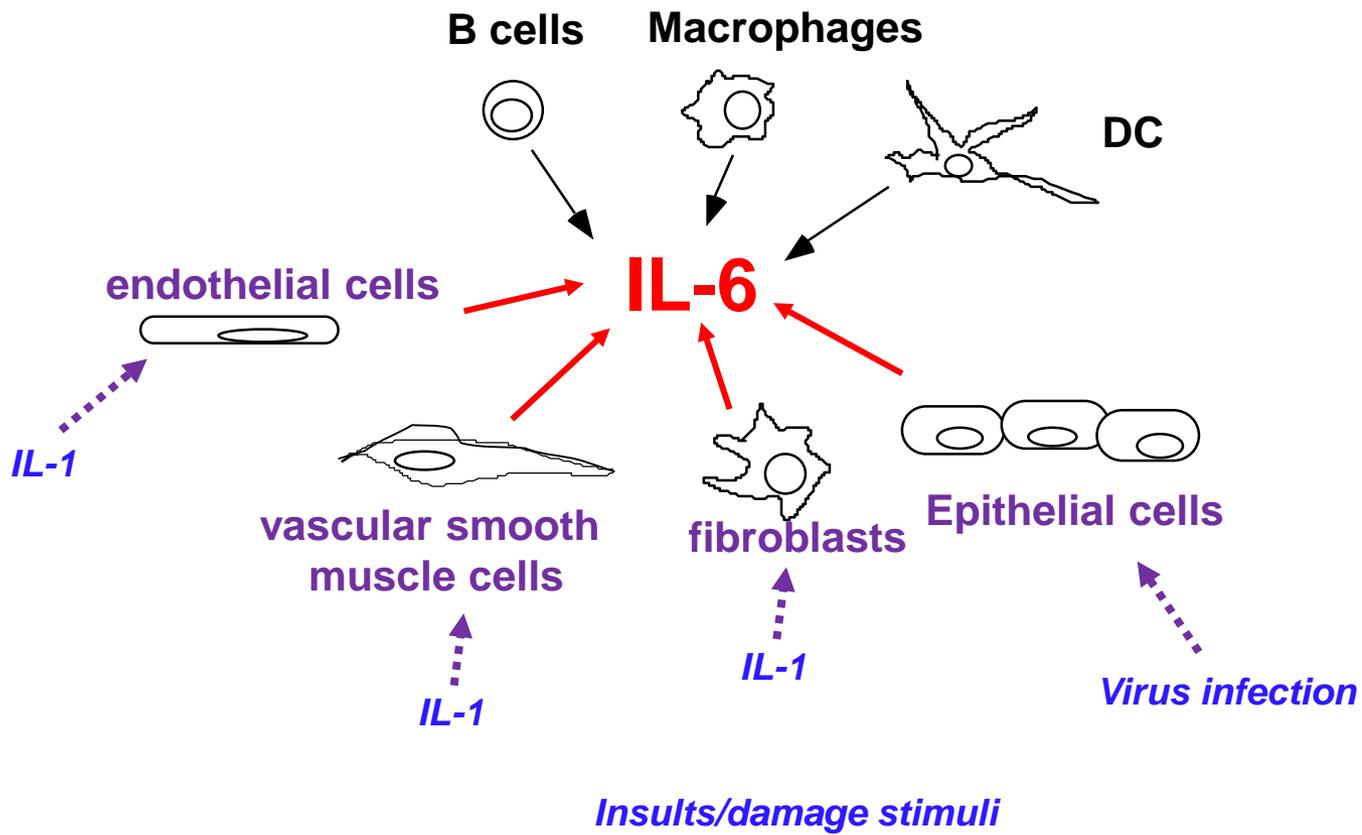


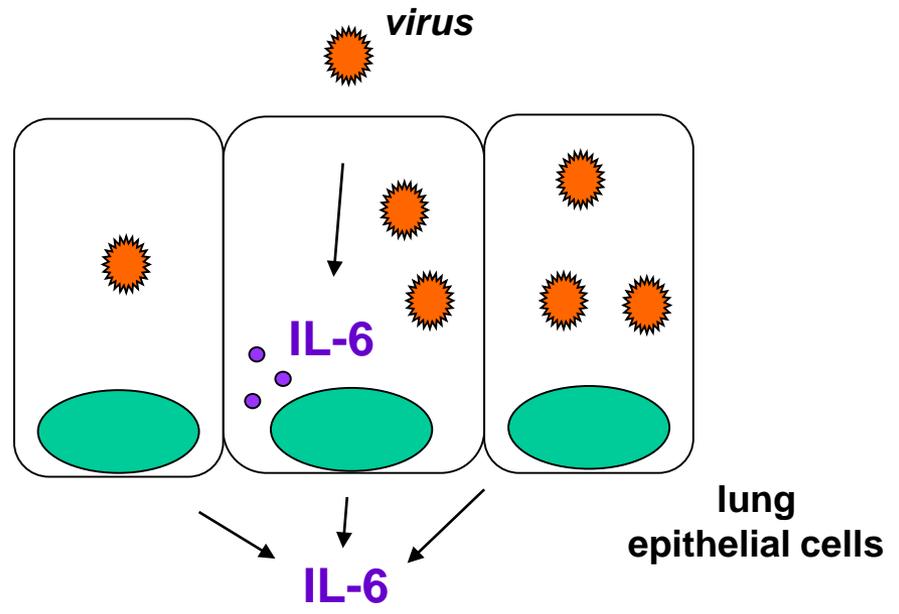
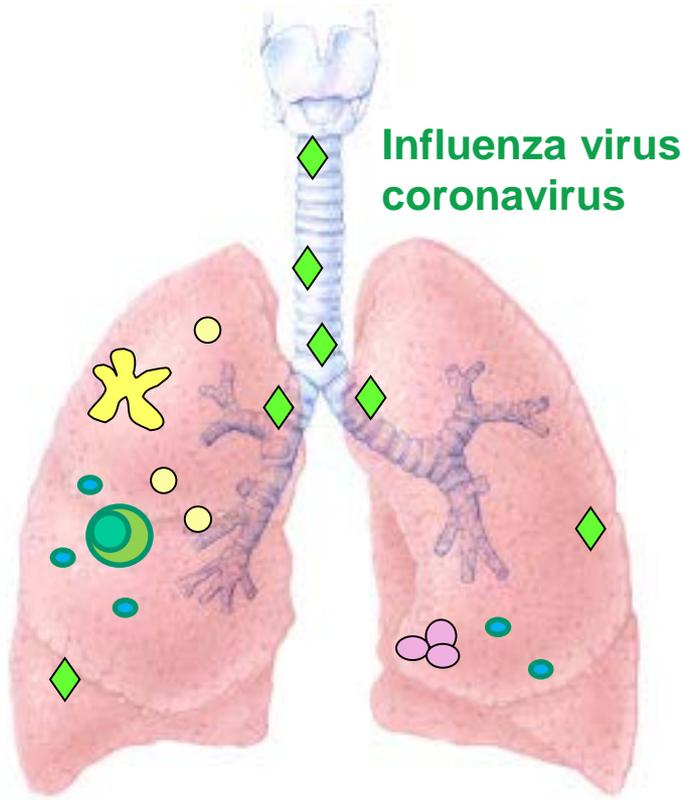
**Treatment with Tocilizumab  
(blocking anti-IL-6R Ab)**  
Tadamitsu Kishimoto, Japan



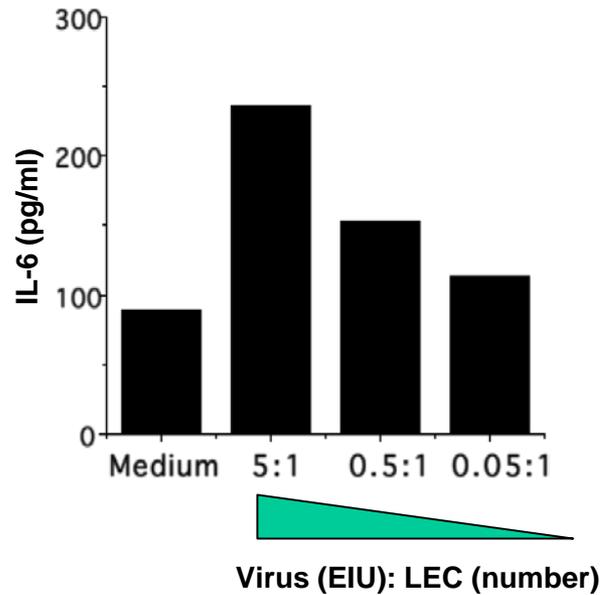
**serum IL-6**

- Crohn's disease
- Rheumatoid Arthritis
- Osteoporosis
- JCA
- SLE

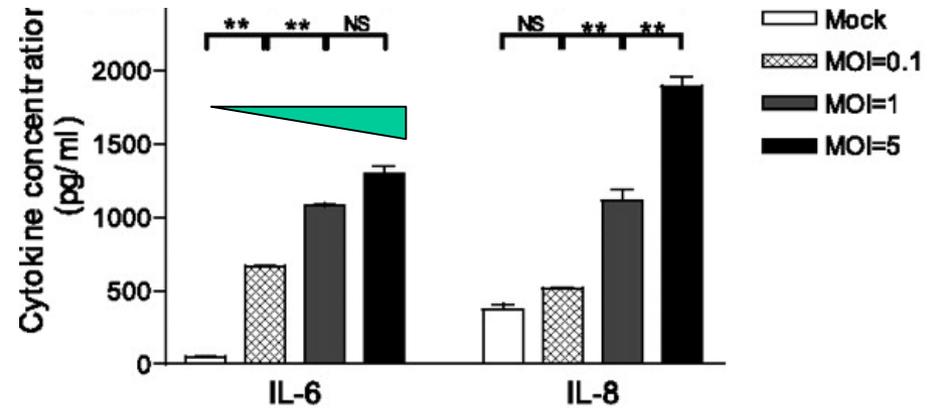




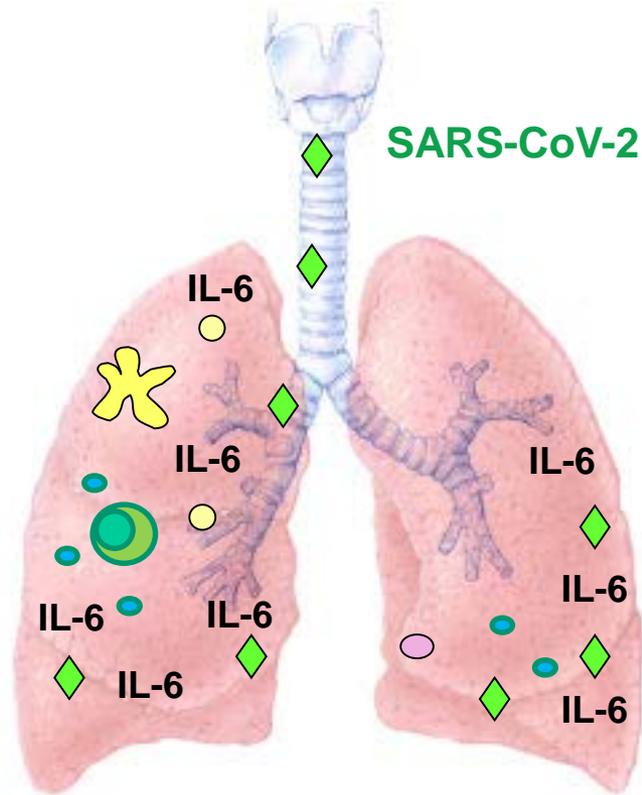
*Influenza virus induces IL-6 production in mouse lung epithelial cells*



*SARS-CoV induces IL-6 production in human lung epithelial cells*



Yoshikawa et al J. Virology 2009



## Study on COVID-19 patients:

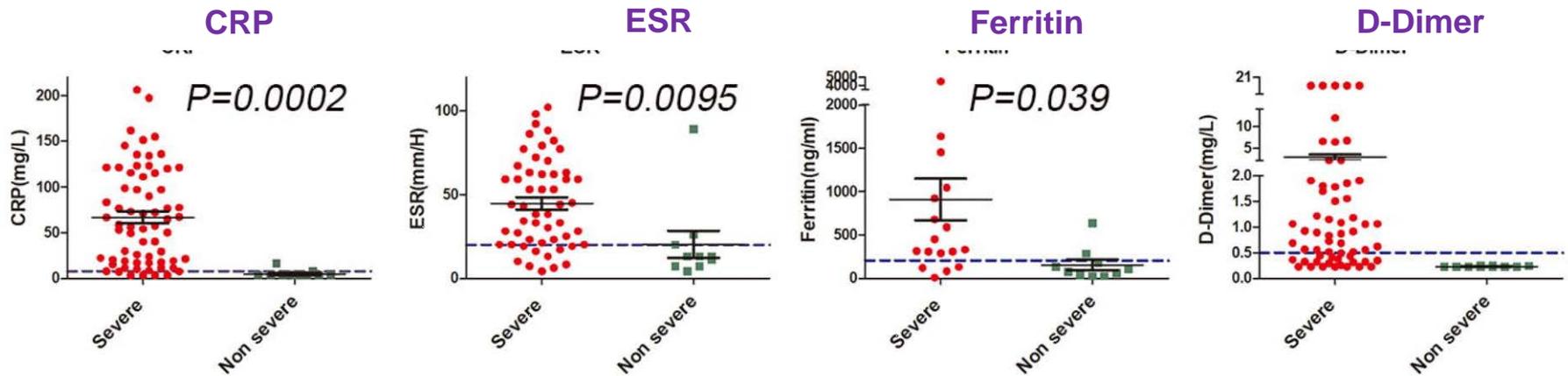
- Use of neutrophil to lymphocyte ratio (NLR): lymphopenia and neutrophilia
- Cytokine Analysis in Serum between non-severe and severe cases
  - increased IL-6 levels (normal TNF levels) in serum in severe relative to non-severe patients

	NLR <sup>high</sup>		NLR <sup>low</sup>	
	Non-severe	Severe	Non-severe	Severe
IL-2, pg/ml	3.3 (3.0-4.1)	3.2 (3.1-3.5)	3.3 (3.0-3.8)	3.2 (3.1-3.3)
IL-4, pg/ml	3.2 (2.9-4.3)	3.3 (2.9-3.6)	3.3 (3.0-4.2)	3.2 (3.0-3.6)
IL-6, pg/ml	5.7 (4.5-12.5)	24.4 (10.2-97.6)*#	6.2 (4.4-8.0)	6.7 (5.5-7.2)
IL-10, pg/ml	5.6 (4.2-7.6)	8.0 (5.7-25.0)	5.1 (4.7-5.8)	5.4 (4.8-5.5)
TNF- $\alpha$ , pg/ml	3.1 (2.9-3.3)	3.2 (2.9-3.2)	2.9 (2.7-3.3)	3.3 (3.2-3.5)
IFN- $\gamma$ , pg/ml	3.6 (2.2-4.3)	3.4 (2.7-4.4)	3.4 (2.4-4.1)	3.6 (2.9-4.0)
Oxygen therapy	29.4 (5/17)	100 (16/16)	18.5 (5/27)	100 (5/5)

## Study on COVID-19 patients:

- Analysis between **non-severe and severe cases upon admission**
  - Baseline CRP, ferritin and D-dimer elevated
  - Baseline immunological parameters were within normal range

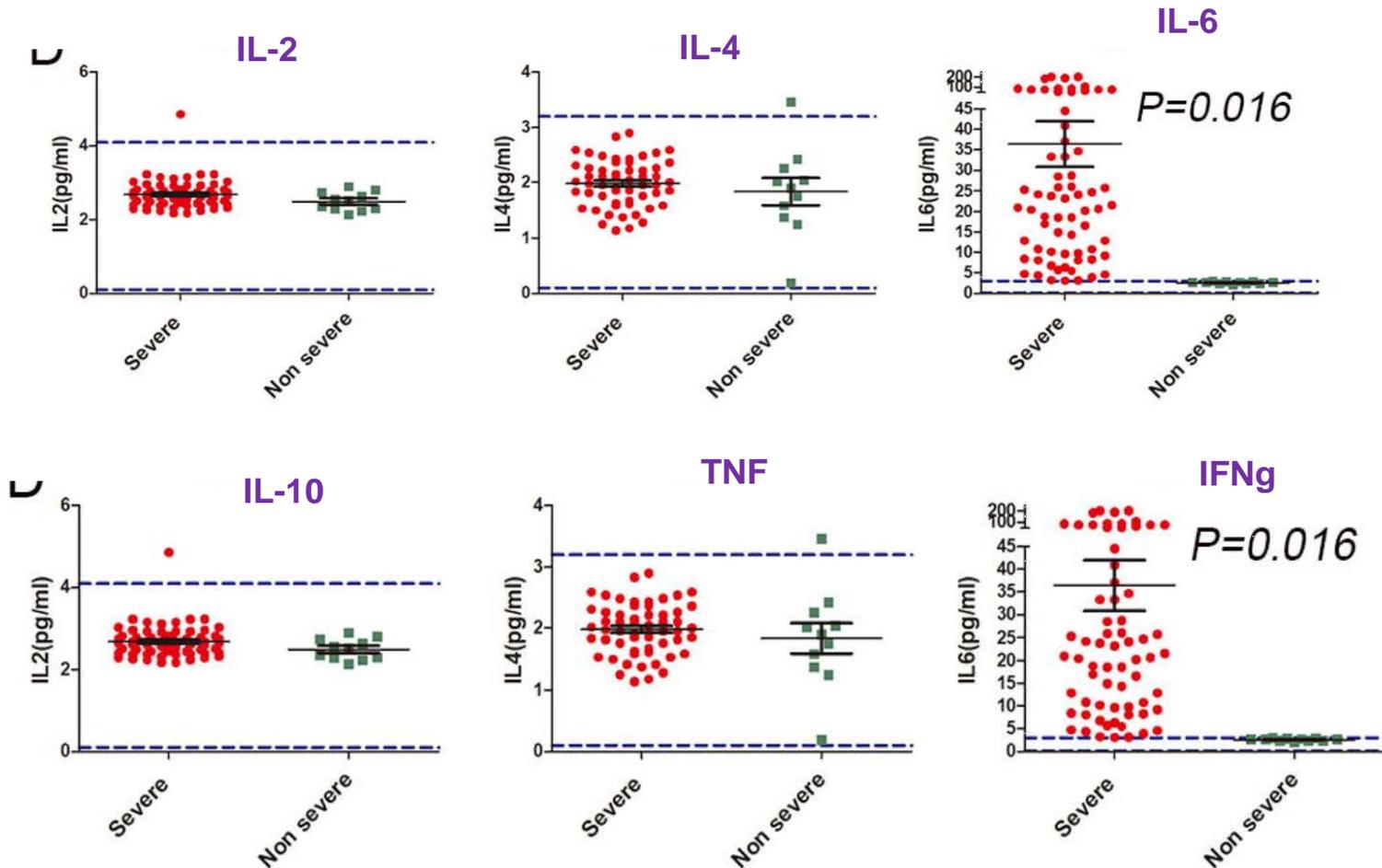
Severe: 69  
Non severe: 11



## Study on COVID-19 patients:

- Analysis between non-severe and severe cases upon admission
  - Baseline CRP, ferritin and D-dimer elevated
  - Baseline immunological parameters were within normal range
  - Baseline IL-6 levels in serum were higher in severe cases

Severe: 69  
Non severe: 11



## Study on COVID-19 patients:

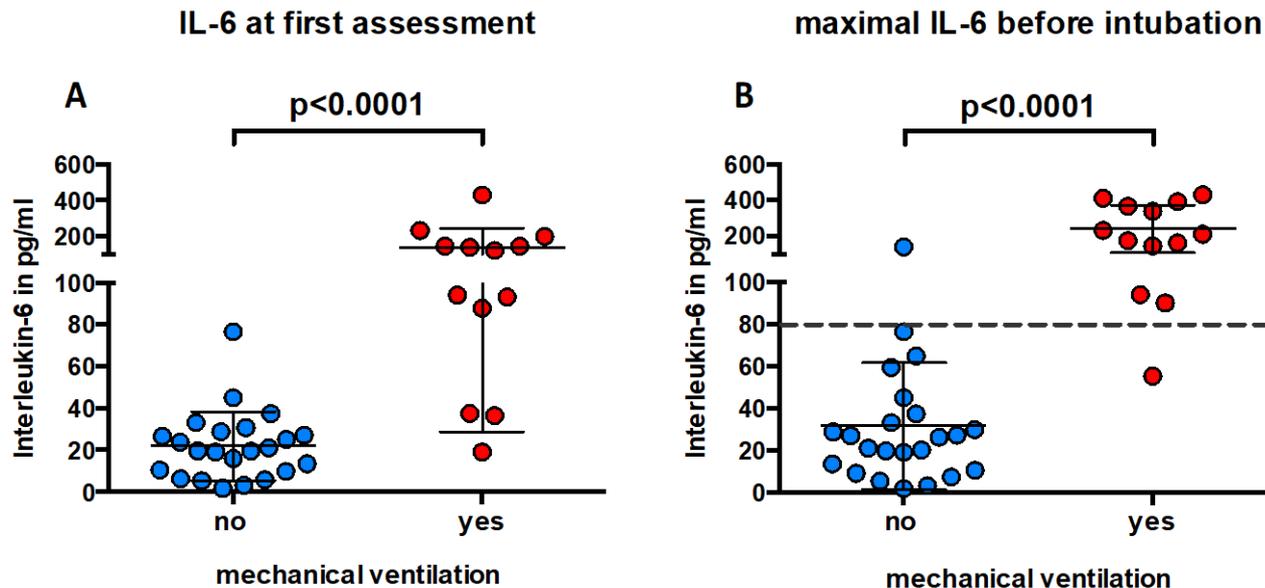
- Analysis between patients requiring **mechanical ventilation or not after admission**
  - No differences in baseline comorbidities, radiological findings, respiratory rate
  - **Baseline IL-6 levels in serum were higher patients requiring mechanical ventilation**

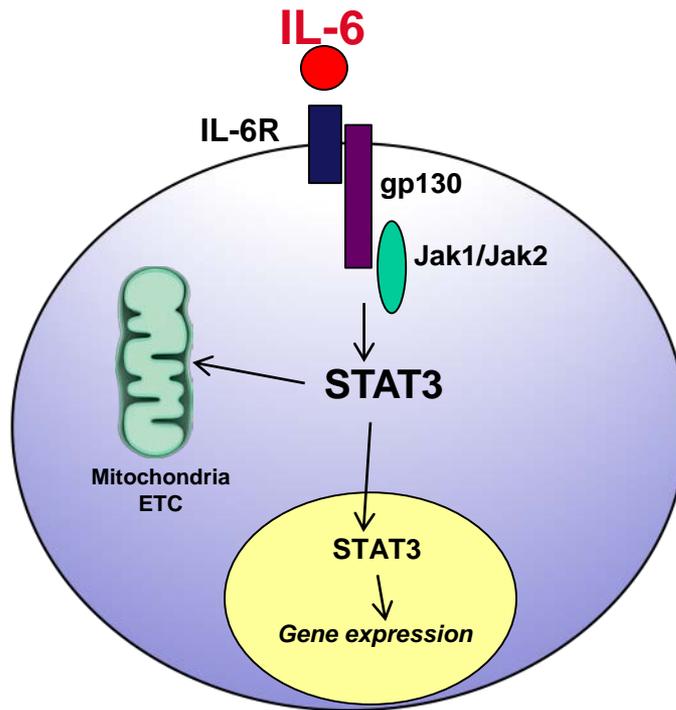
Laboratory parameters	Evaluable	Median (range)	Mechanical ventilation		p-value
			No (n = 27)	Yes (n = 13)	
Lymphocyte count (%)	36	19 (4 - 45)	21 (4 - 45)	15 (6 - 26)	0.050
→ CRP (mg/dl)	40	2.8 (0 - 31.5)	1.7 (0 - 31.5)	7.8 (1.6 - 17.1)	0.0019
Bilirubin (mg/dl)	36	0.5 (0.2 - 1.9)	0.5 (0.2 - 1.2)	0.5 (0.4 - 1.9)	0.93
WBC (G/l)	40	5.295 (2.12 - 308)	4.75 (2.12 - 12.5)	6.64 (4.99 - 308)	0.0014
LDH (U/l)	38	292 (182 - 1078)	281 (182 - 619)	346 (252 - 1078)	0.0026
PCT (ng/ml)	37	0 (0 - 5)	0 (0 - 0.6)	0.1 (0 - 5)	0.011
→ IL6 (pg/ml)	37	27.1 (0 - 430)	19.6 (0 - 76.5)	121 (19.2 - 430)	0.000012
Thrombocyte count (G/l)	40	165 (88 - 440)	186 (88 - 334)	160 (1 - 440)	0.59
Troponin T (ng/ml)	34	0 (0 - 0.032)	0 (0 - 0.022)	0 (0 - 0.032)	0.018
Creatinine (mg/dl)	40	0.9 (0.4 - 2.1)	0.9 (0.4 - 1.3)	1.0 (0.9 - 2.1)	0.00034
→ D-Dimer	30	0.7 (0 - 2.9)	0.6 (0 - 2.2)	1.1 (0.6 - 2.9)	0.028
Ferritin (ng/ml)	27	644 (64 - 2153)	606 (64 - 1748)	810 (431 - 2153)	0.16

## Study on COVID-19 patients:

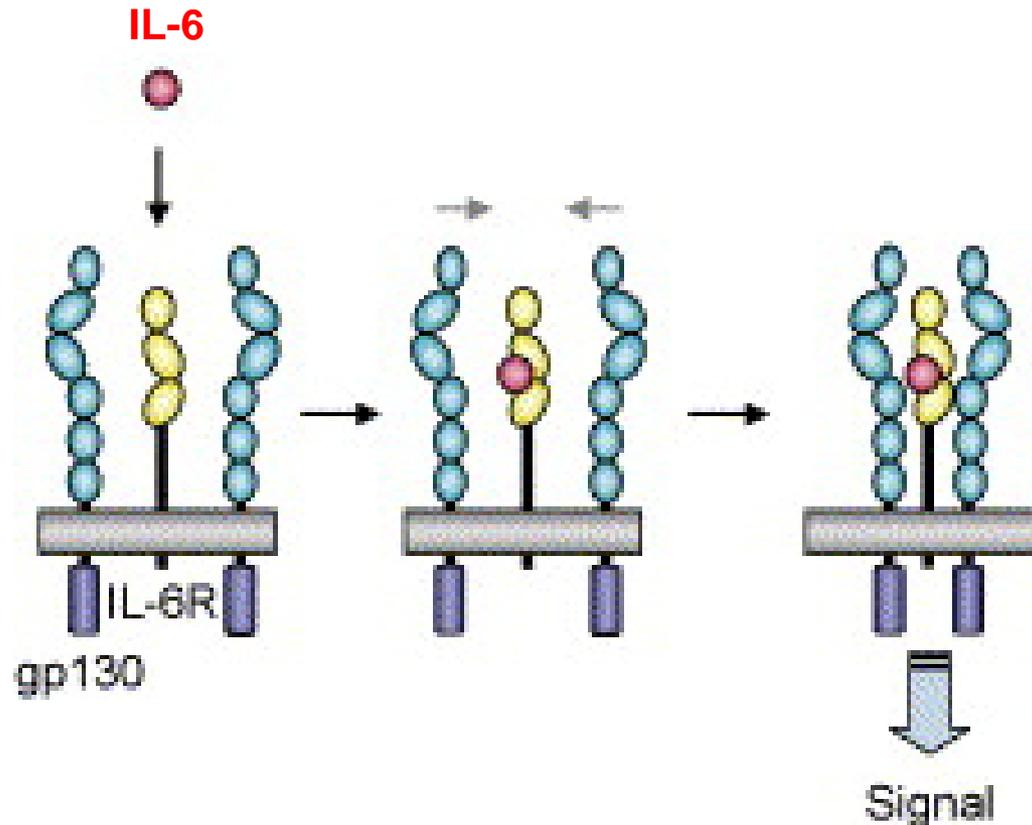
### -Analysis between patients requiring **mechanical ventilation or not after admission**

- No differences in baseline comorbidities, radiological findings, respiratory rate
- Baseline immunological parameters were within normal range
- **Baseline IL-6 levels in serum were higher patients requiring mechanical ventilation**
- **Maximal IL-6 level for each patient during disease predicts respiratory failure**
- **Risk of respiratory failure for patients with IL-6  $\geq 80$  pg/ml was 22 times higher compared with patients with lower IL-6 levels**





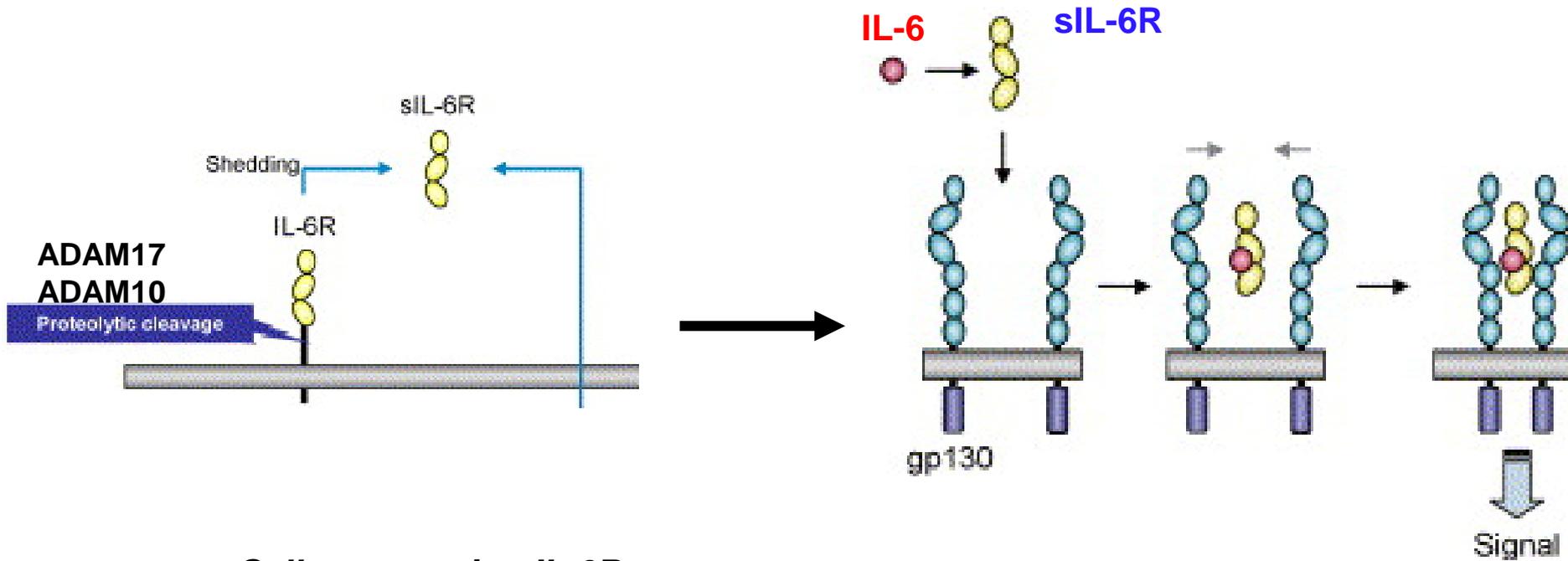
## Classical IL-6 signaling (use of transmembrane IL-6R)



Cells expressing IL-6R:

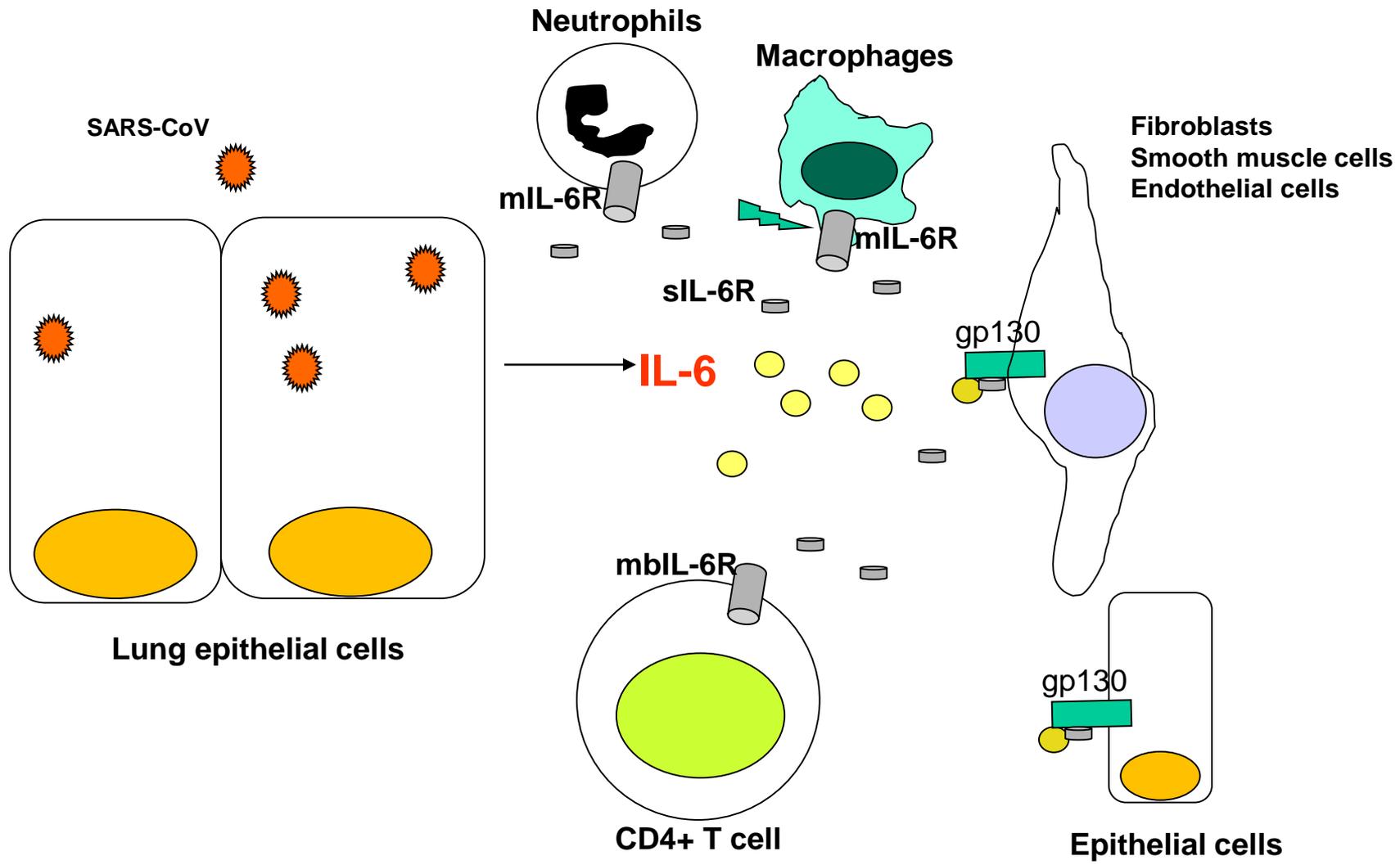
- hematopoietic cells (CD4 and CD8 T cells, macrophages, neutrophils...)
- hepatocytes

## IL-6 trans-signaling (use of soluble IL-6R)



**Cells expressing IL-6R**  
(macrophages, neutrophils, CD4 cells)

**Cells lacking IL-6R**  
(epithelial cells, smooth muscle cells, endothelial cells etc)



### *Effects of IL-6 on multiple types of cells,*

- promotes survival of neutrophils
- promotes proliferation and migration of vascular smooth muscle cells
- endothelial dysfunction
- induces fibrinogen synthesis (CVD)
- induces collagen production in fibroblasts
- induces acute phase response
- regulates CD4 and CD8 T cell function

### *Association of IL-6 with multiple diseases*

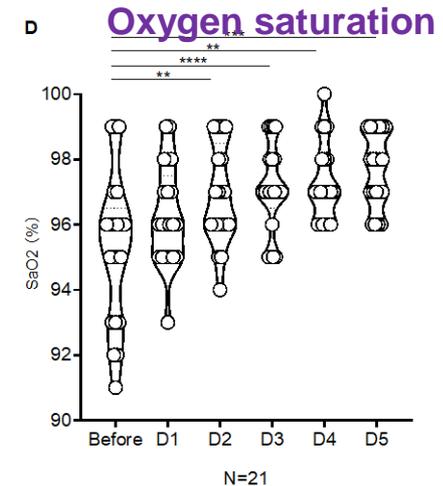
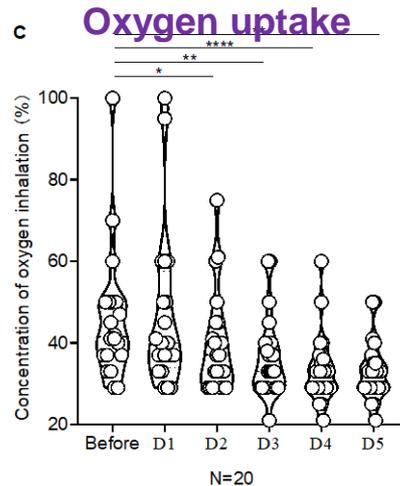
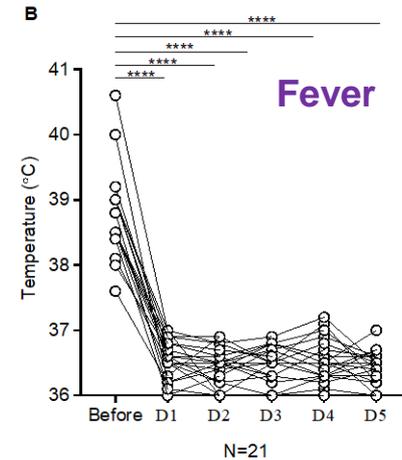
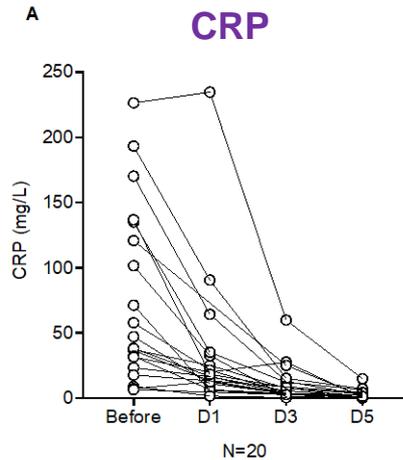
- autoimmune disease (e.g. RA)
- diabetes
- pulmonary hypertension (poor survival)
- heart failure
- asthma, COPD, lung fibrosis
- Kidney diseases
- etc

# Treatment of COVID-19 patients with a blocker of IL-6R (tocilizumab) in a single-arm trial:

## Tocilizumab treatment outcomes:

- CRP levels decreased to normal levels in 84% of the patients after 5 days
- Fever returned to normal within 1 day
- Peripheral oxygen saturation improved rapidly
- 1 patient was taken off the ventilator after 1 day, 1 extubated patient regained consciousness after 5 days
- 15 patients lowered their oxygen intake

21 patients



## ***Inhibiting IL-6/IL-6R signaling therapeutically in COVID-19***

- **Tocilizumab**. Blocking IL-6R (membrane and sIL-6R) antibody
- **Sarilumab**. Blocking IL-6R (membrane and sIL-6R) antibody
- **Jak1/Jak2 inhibitors**: Baracitinib,
- **Blockers for IL-1**.

*Is there any genetic component that could influence severity of COVID-19?*

*?????????*

### ***IL-6 gene polymorphisms:***

- ***-174 G>C in the IL-6 gene promoter***
- ***“C”, minor allele (CC about 20% of population but varies),***
- ***CC is associated with lower IL-6 levels in plasma,***
- ***CC associated with decrease risk of type 2 diabetes***

### ***IL-6R gene polymorphisms:***

- ***Rs2228145 Asp<sup>358</sup>Ala (A>C) in coding region (exon 9).***
- ***“C” is the minor allele (10-15% population)***
- ***“C” - increased production of sIL-6R (increased cleavage)***
- ***“C” - association with risk of asthma and impaired lung function***

***Levels of IL-6 in serum are lower in females versus males***

- ***both in mouse and human***

***Elevated levels of IL-6 in serum with aging***

## ***IL-6 in COVID-19, overall summary:***

- ***High IL-6 levels correlate with severity of disease in COVID patients***
- ***IL-6 levels do not necessarily represent an exaggerated immune response (no TNF increase)***
- ***IL-6 most likely comes from lung epithelial cells (virus replication), vascular smooth muscle cells (IL-1) and other lung cells***
- ***blocking IL-6R in hospitalized severe patients is a promising therapy that could reduce the use time for ventilators and potentially save lives.***