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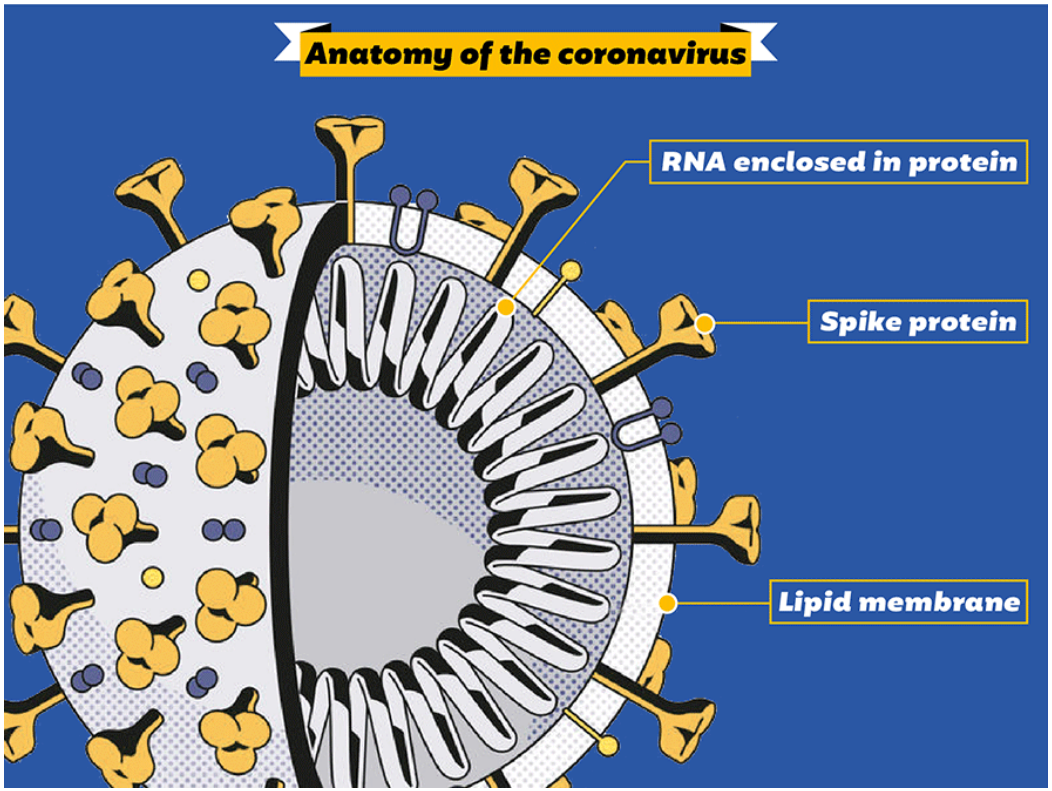
Why should we be worried?



Disease	MERS	SARS	COVID-19
Outbreaks	2012, 2015 2018	2002-2004	2019-2020
Epidemiology			
Confirmed cases	2494	8096	7,930,989
Deaths	858	774	433,783
Case fatality rate	37%	9.2%	5.5%

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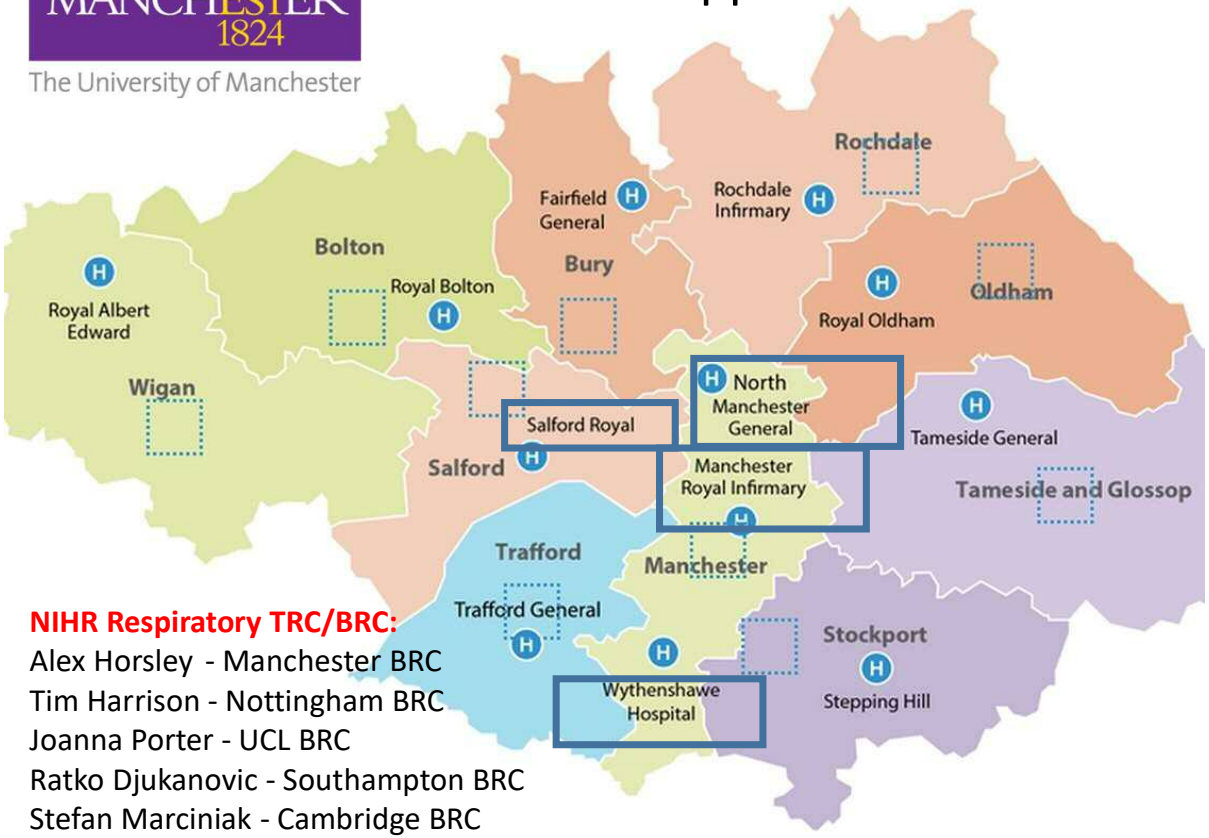
The CIRCO approach



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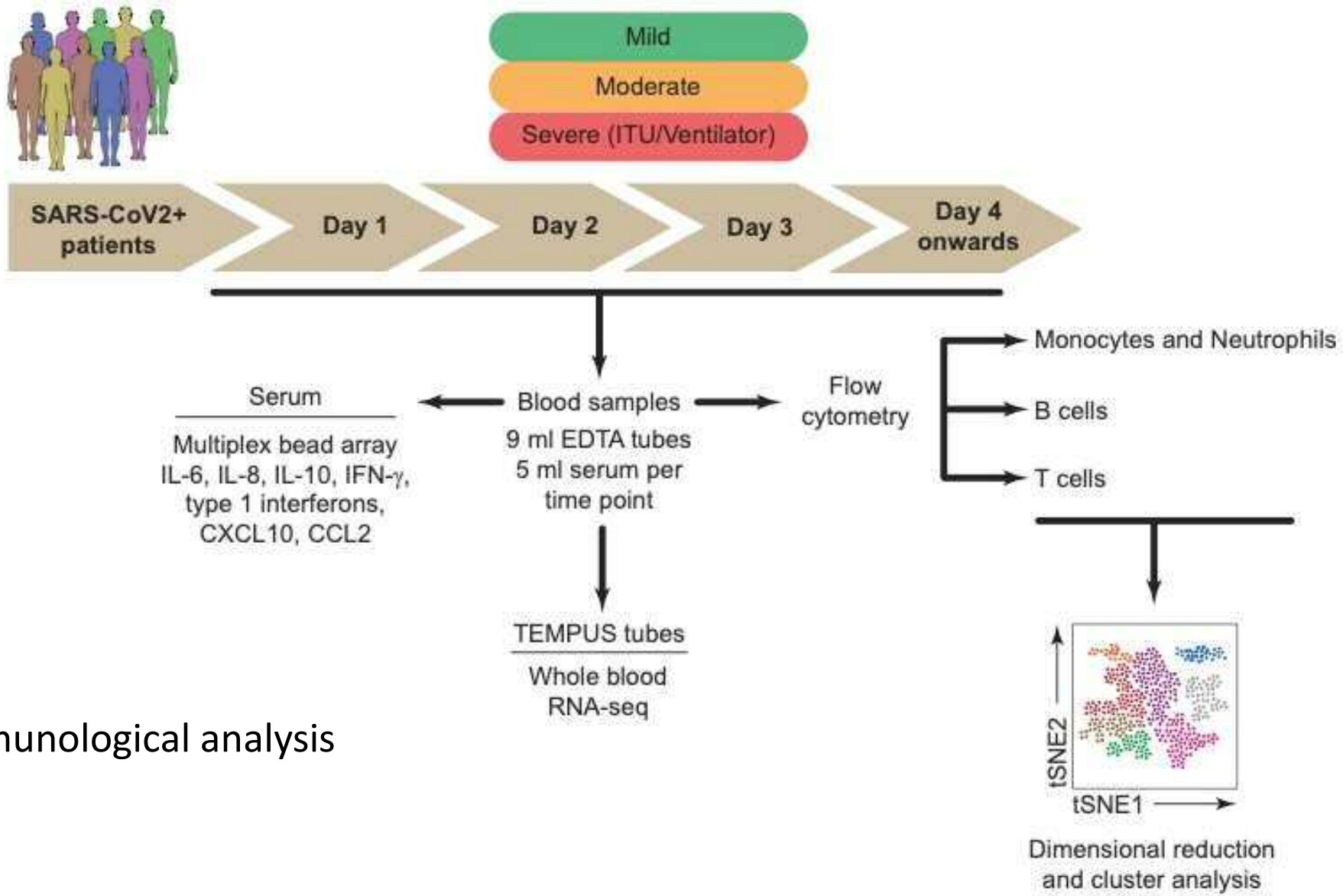

Real-time immunological analysis

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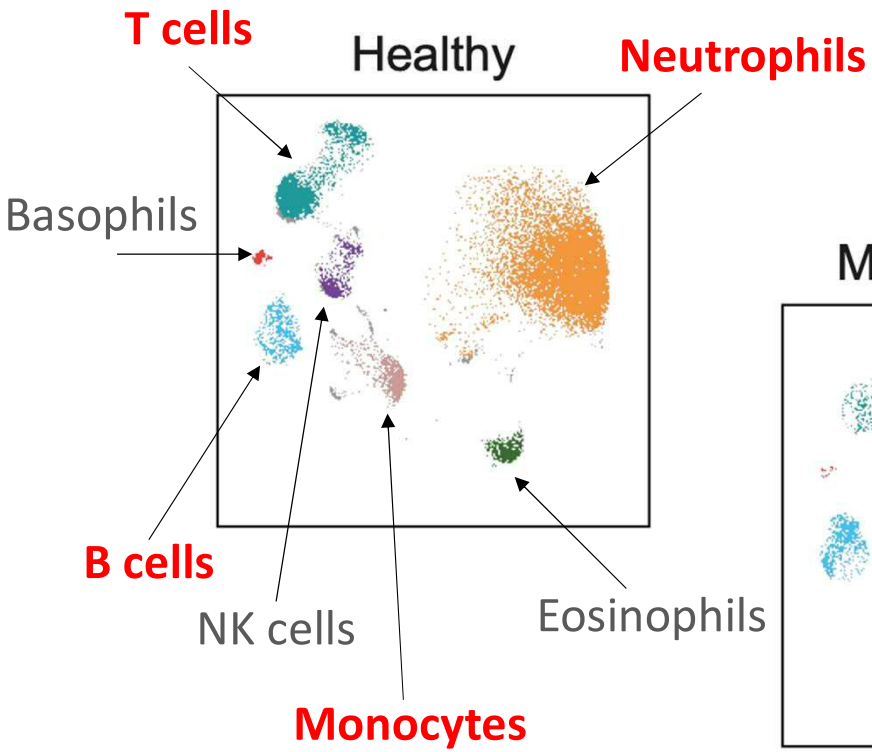
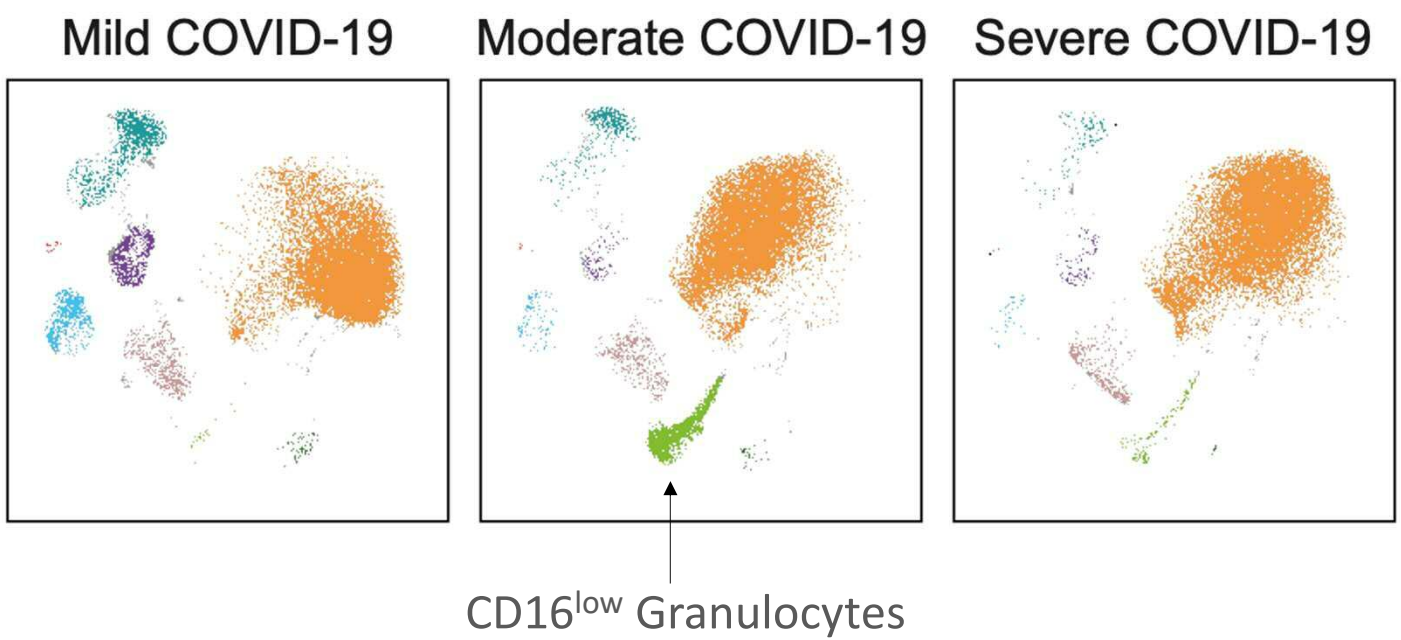
Global alterations to innate and adaptive immune cells visualised by UMAP in fresh whole blood samples

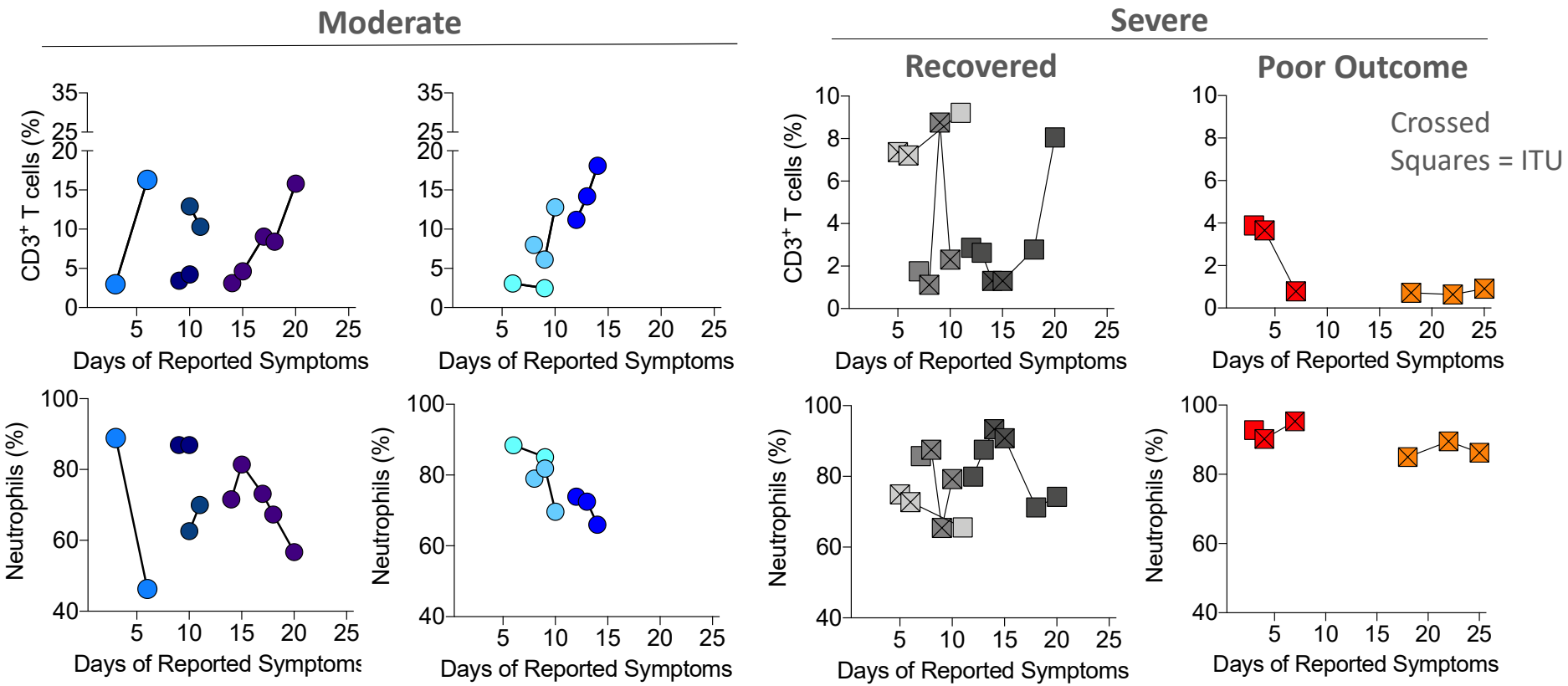


17-parameter Flow cytometry

Markers associated with distinct immune populations and activation

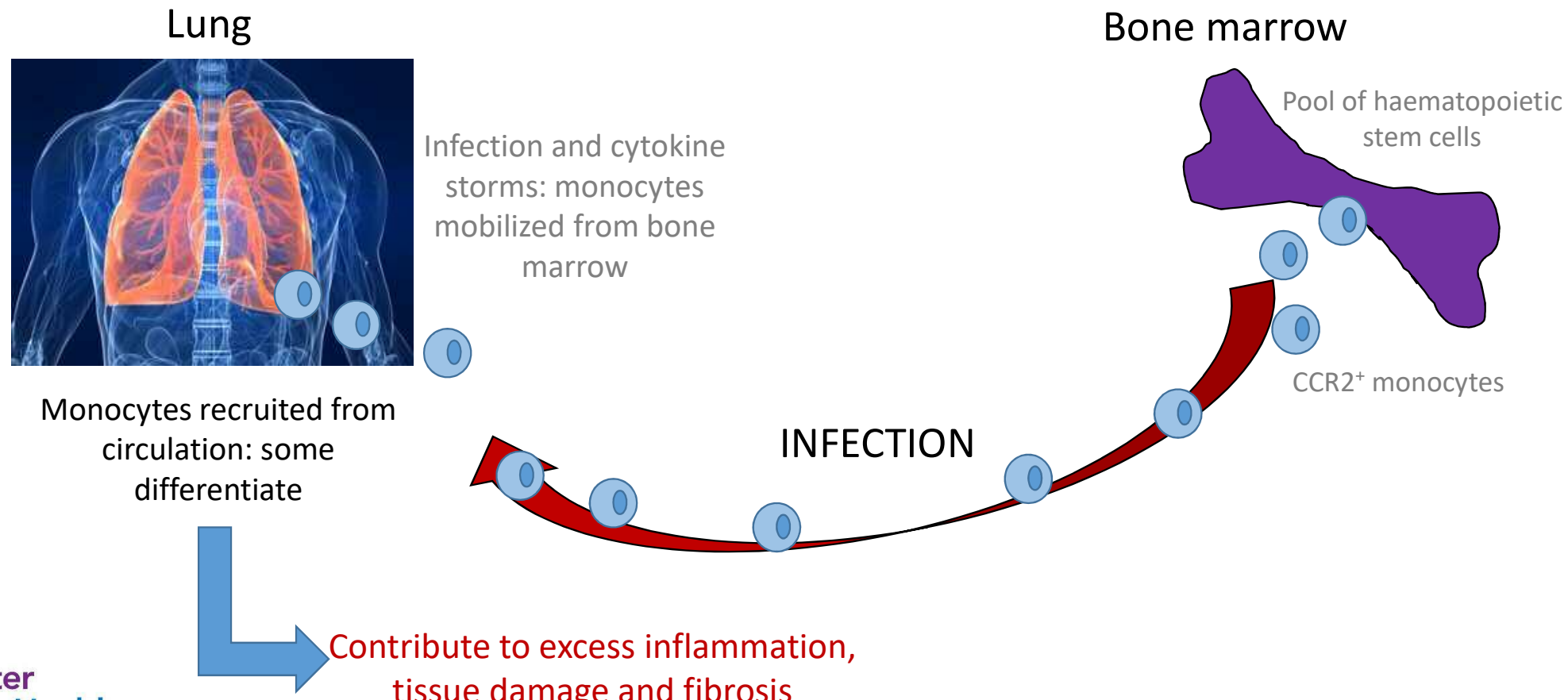


Restoration of balance of T cells and neutrophils is associated with good outcome



Trajectory of immune profile for mild patients similar to those with moderate disease

Monocytes play a critical role in respiratory infections



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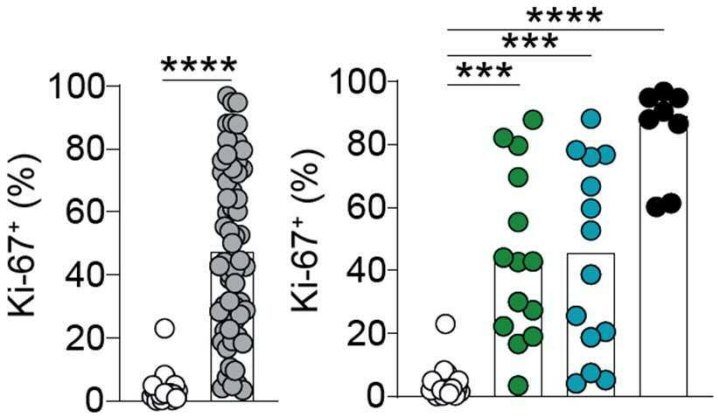
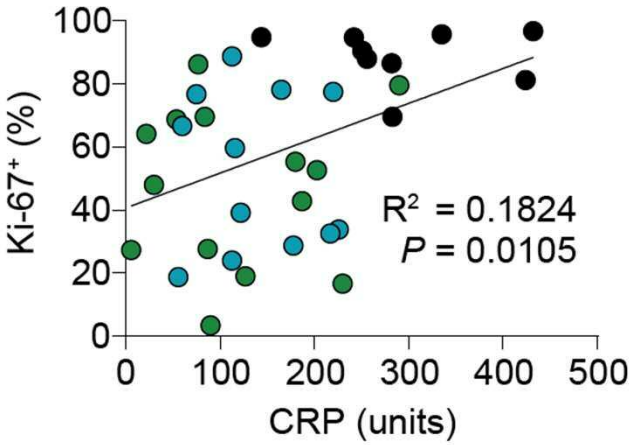
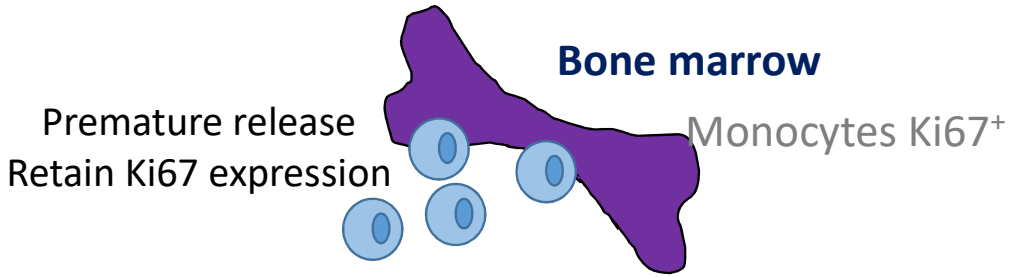
Enhanced expression of cell cycle marker Ki67 in COVID-19 monocytes upon admission







Emergency myelopoiesis?

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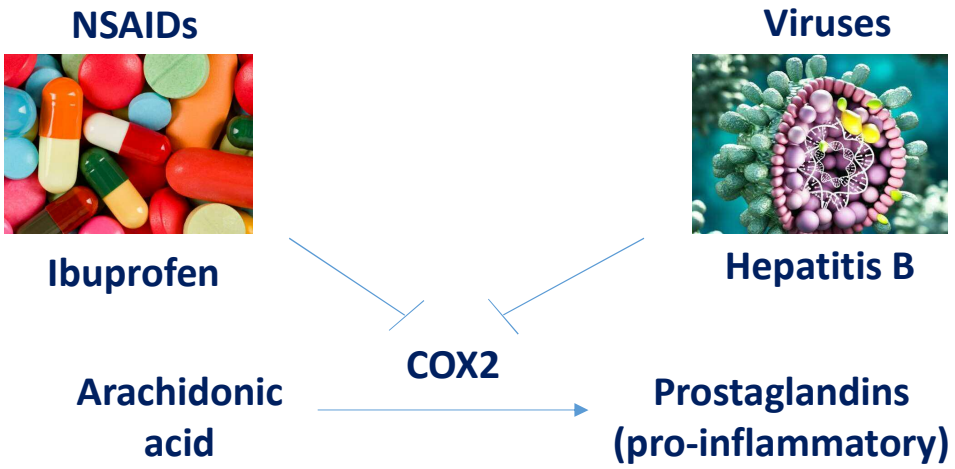
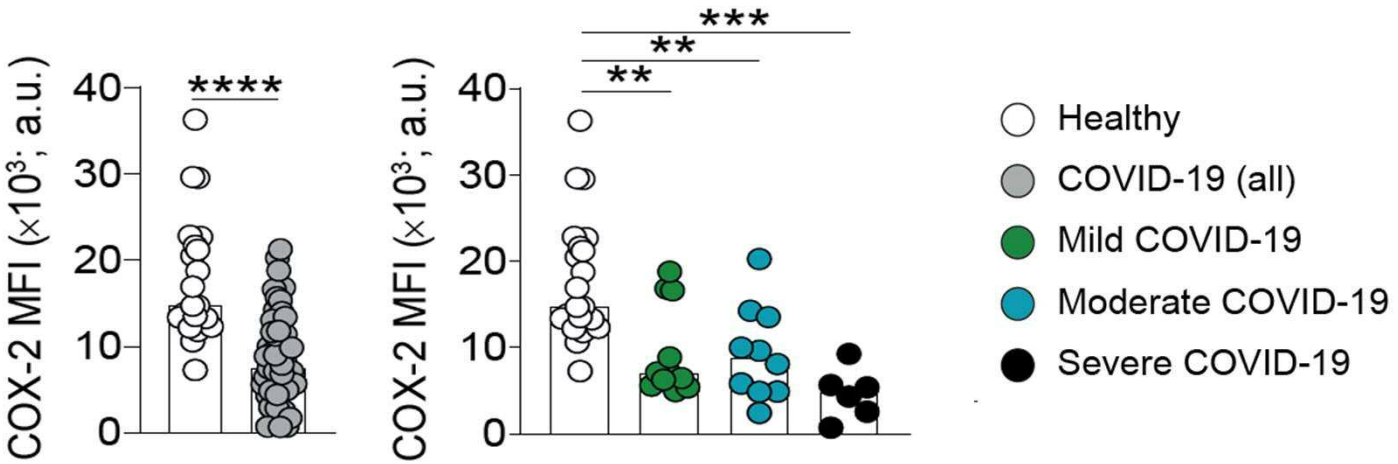
Reduced expression of cyclo-oxygenase 2 (COX2) in COVID-19 monocytes





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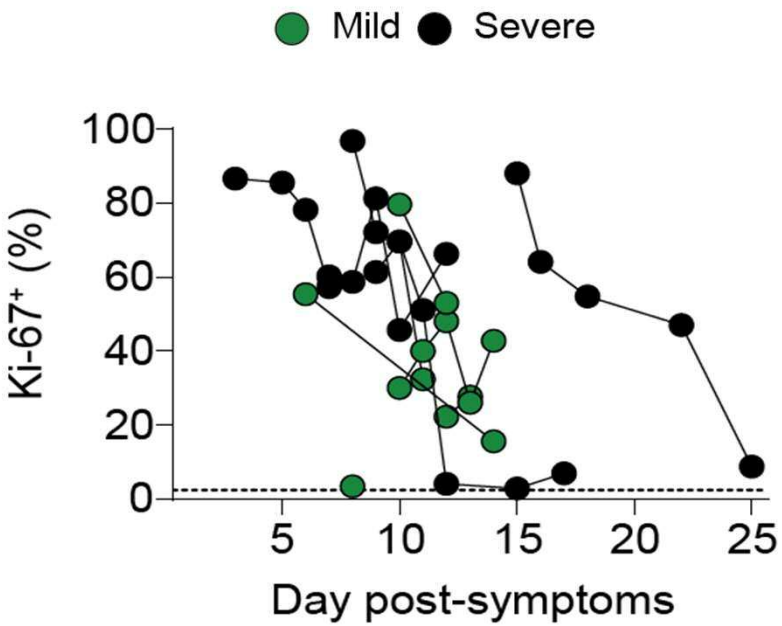
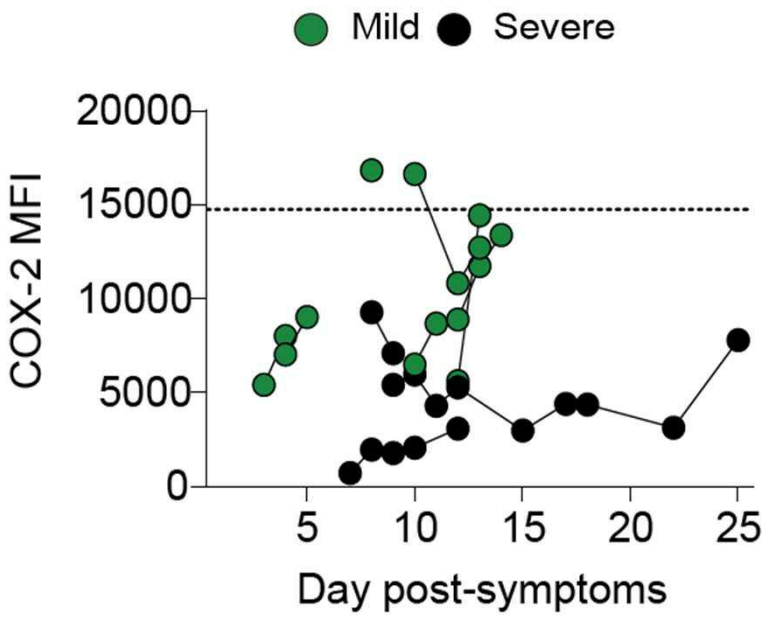
What happens to monocytes throughout the COVID-19 disease course?



Ki67 drops rapidly regardless of disease outcome: early severity predictor



COX2 increases with recovery, stays low during ITU

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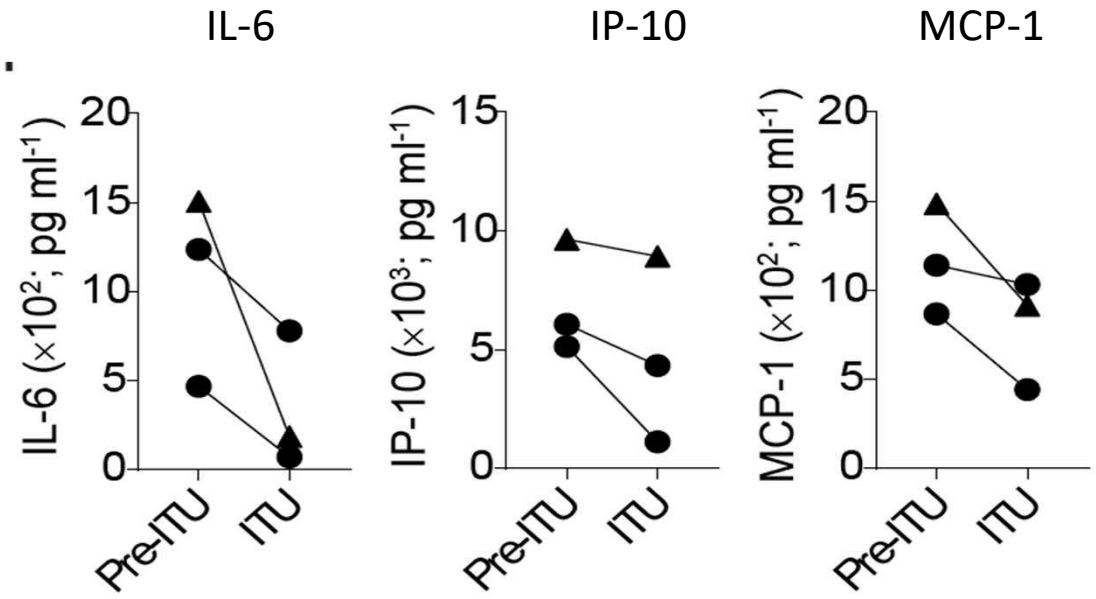
What happens to cytokine storm throughout the COVID-19 disease course?

Systemic cytokines drop soon after ITU admission



Inflammatory: Innate cells

Innate cell migration

Innate cell migration

Structural and physiological damage in ITU: critical window for targeting immune response early after admission

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Infection fatality ratio by age group

Age	Median	95% CrI (lower)	95% CrI (upper)
<1year,1-4	0.00045%	7.8e-05%	0.002%
5-14	0.0013%	0.00071%	0.0023%
15-24	0.0043%	0.0029%	0.0062%
25-44	0.029%	0.025%	0.034%
45-64	0.44%	0.4%	0.49%
65-74	2.9%	2.6%	3.2%
75+	17%	14%	22%

Birrel P, et al. (2020). COVID-19:nowcast and forecast. https://www.mrc-bsu.cam.ac.uk/now-casting/ (Accessed: 14/07/2020)

Patient details:

	All patients (49)	Mild (18)	Moderate (21)	Severe (10)
Age	61 (51 – 71)	61.5 (45 – 72.5)	59 (51 – 68)	66 (52 – 72.5)
Sex				
Male	31 (63.3%)	11 (61.1%)	13 (62%)	7 (70%)
Female	18 (36.7%)	7 (38.9%)	8 (38%)	3 (30%)
BMI	27.5 (24.9 - 30)[4]	27.1 (23.6 - 30)[1]	28.3 (25.7 - 30)[2]	26.5 (24.9 – 30.4)[1]
Co-morbidity				
Diabetes	8/49 (16.3%)	3/18 (16.7%)	2/21 (9.5%)	3/10 (30%)
IHD	5/49 (10.2%)	2/18 (11.1%)	1/21 (4.8%)	2/10 (20%)
HTN	14/49 (28.6%)	5/18 (27.8%)	7/21 (33.3%)	2/10 (20%)
COPD	9/49 (18.4%)	4/18 (22.2%)	4/21 (19.1%)	1/10 (10%)
Asthma	5/49 (10.2%)	2/18 (11.1%)	3/21 (14.3%)	0/10 (0%)
Malignancy	3/49 (6.1%)	0/18 (0%)	1/21 (4.8%)	2/10, (20%)

So what? Our results have clinical implications:

Disease severity is driven by the innate immune system

Patients who go on to have severe COVID-19 can be identified on admission: High Ki-67, Low COX-2, Low T cells, High neutrophils

The cytokine storm abates prior to ITU

Use of non-steroidal anti-inflammatory drugs (NSAIDs) would compound the already low COX-2

Recommended therapeutics:

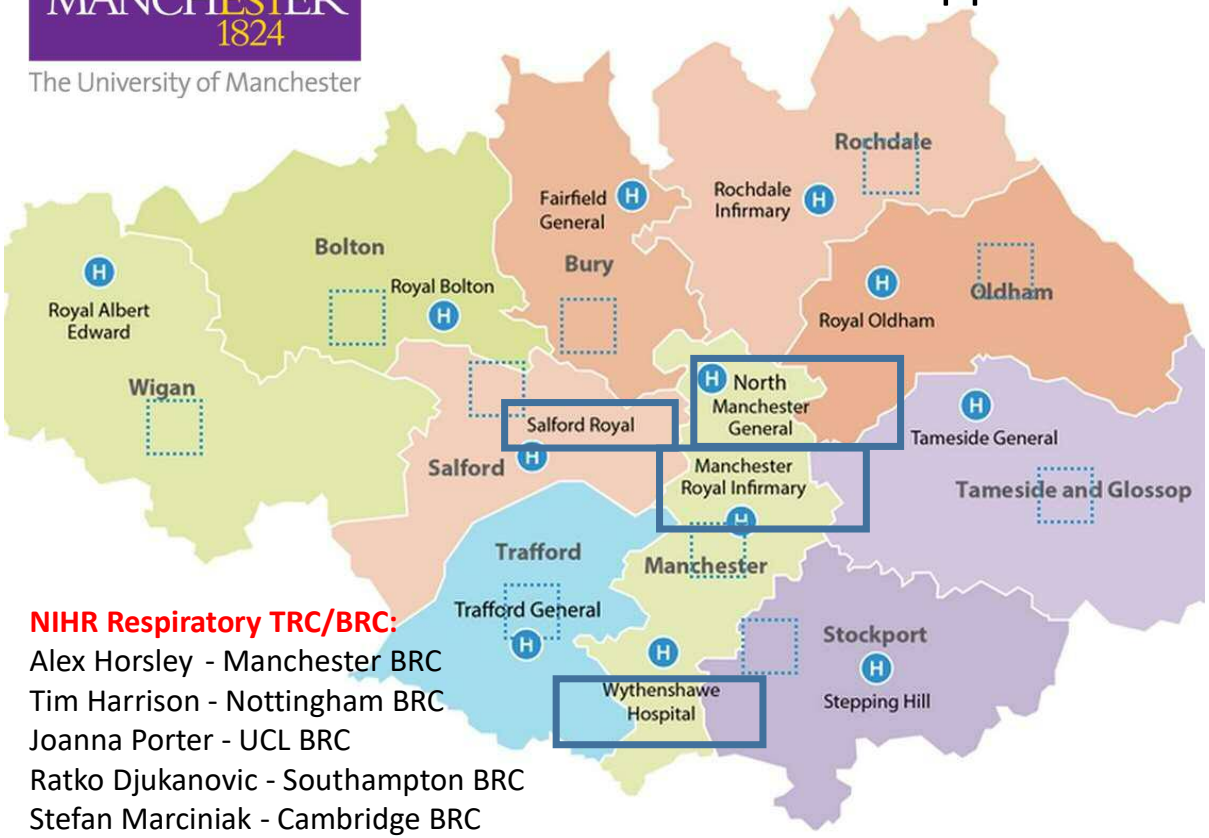
To stop recruitment of immune cells: complement anaphylatoxin C5a or IL-8 (CXCL8)

To stop bone marrow release: Inhibit CXCR2

To stop neutrophil survival: , neutrophil elastase inhibitors and inhibition of G-CSF, IL-23

To reduce neutrophil effects: Target toxic products such as S100A1/A2, HMGB1 and free radicals, formation of NETS

The One Manchester approach



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