Drexel MEDICINE

PLASMA AND THE IMMUNE SYSTEM

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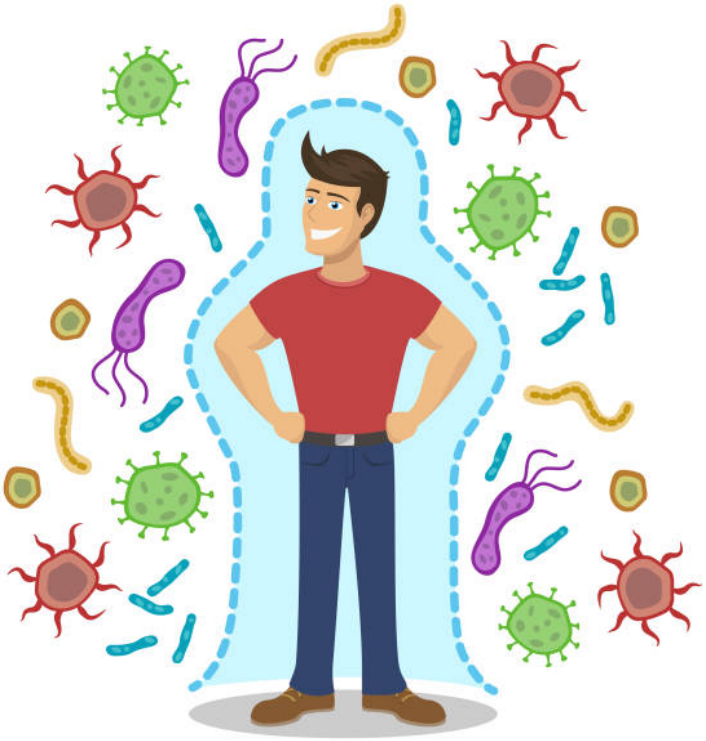
https://cdn.cancercenter.com/-/media/ctca/images/others/blogs/2017/10-october/04-blog-immune-system-l.jpg

Immune System

- Host defense system
- Protects against disease

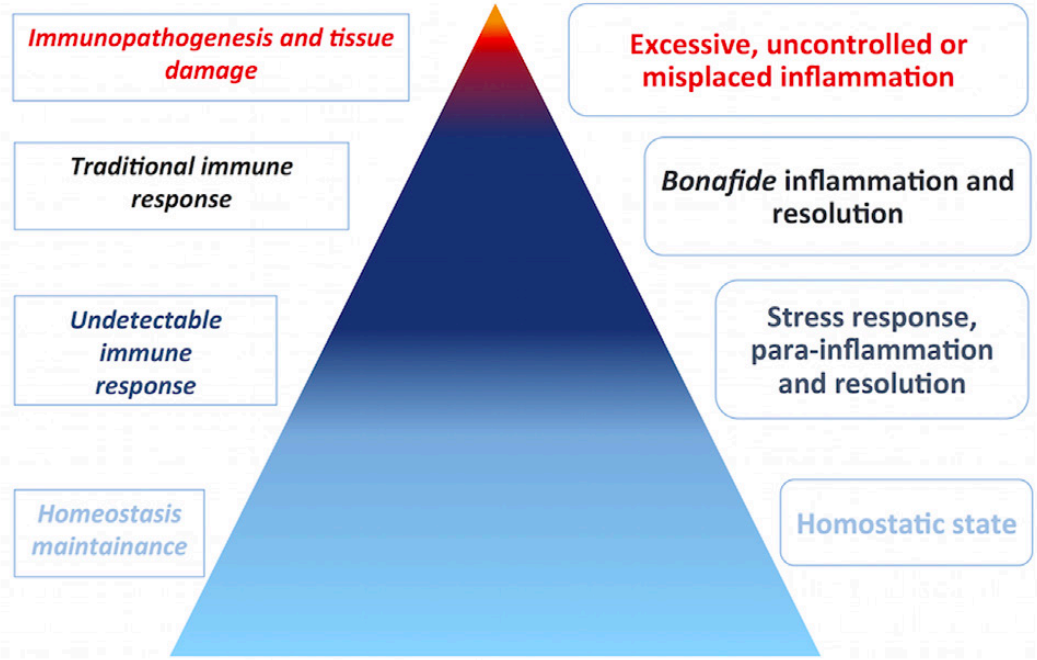
HEALTHY IMMUNE SYSTEM

- Distinguish self from non-self
  - ✓Tolerate self
  - ✓Reject non-self (infectious agents)
    - What about normal flora?
  - ✓Reject altered self (diseased cells)



Immune System

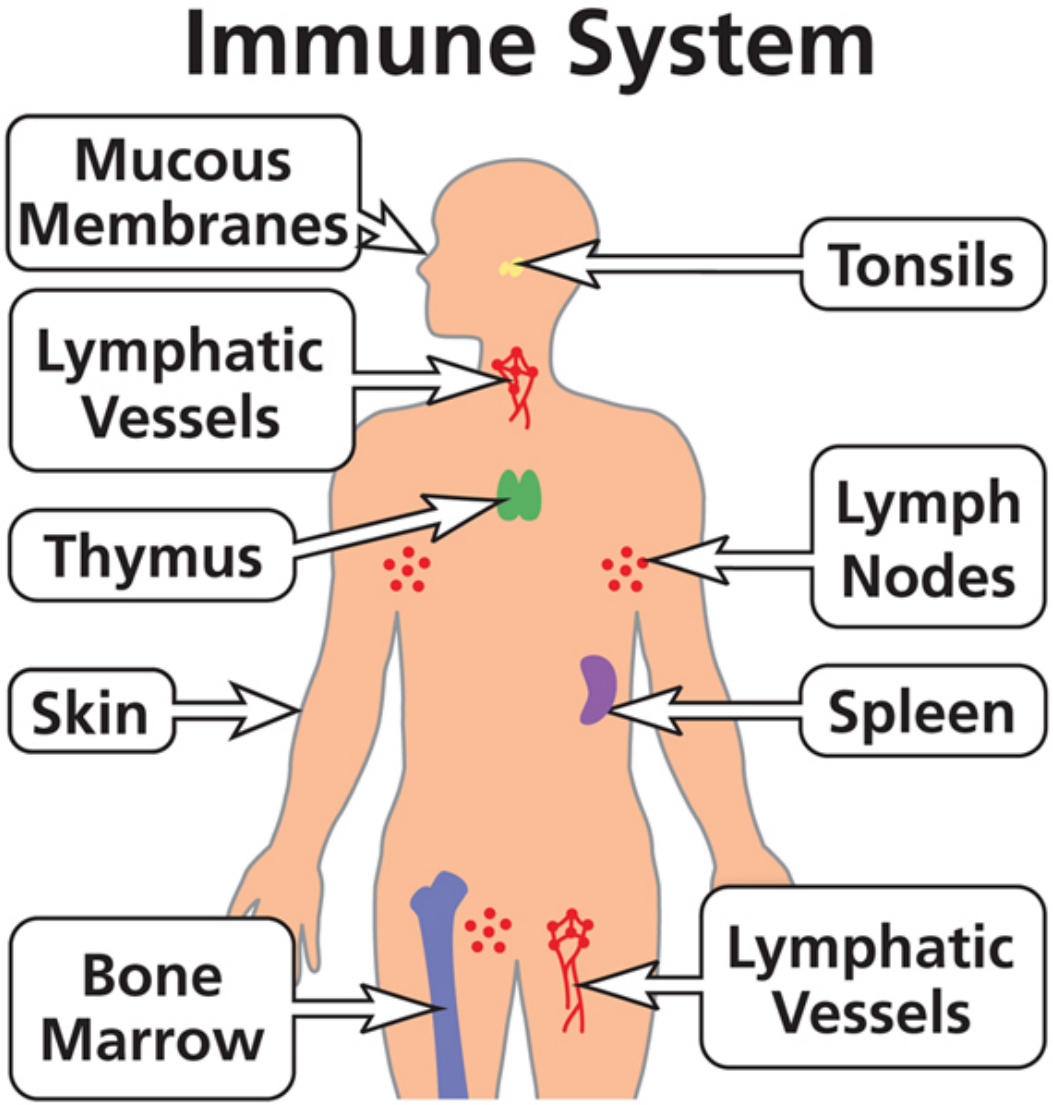
Disease is a rare phenomenon!



Maintains homeostasis!!!

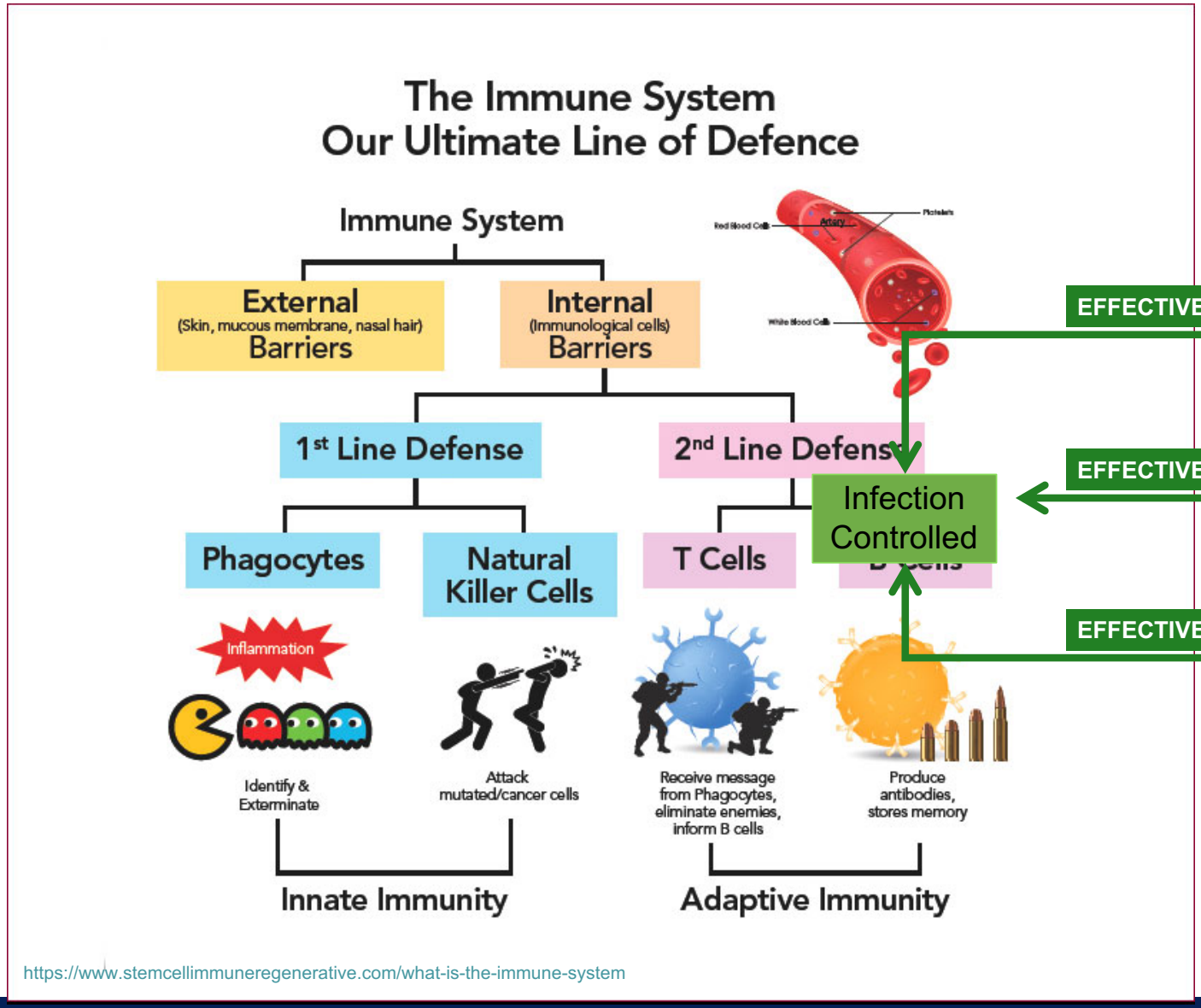
doi: 10.3389/fimmu.2016.00125

Immune System

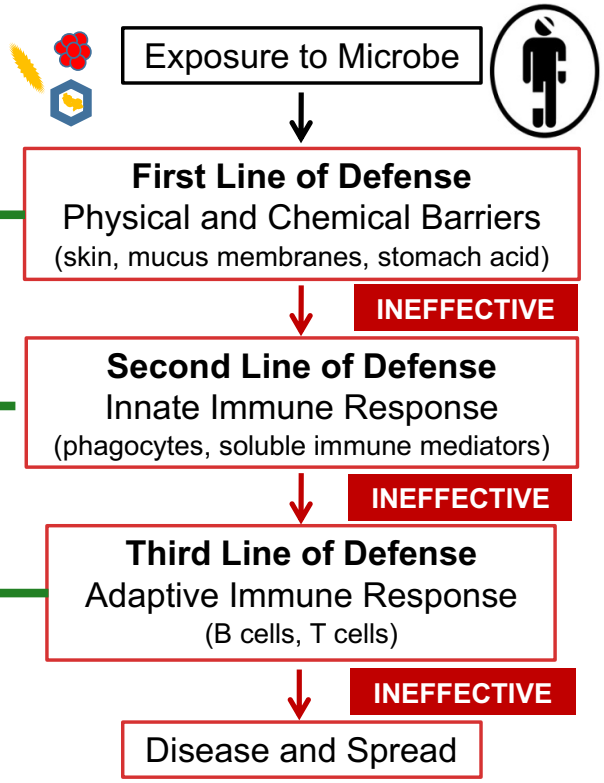


https://aidsinfo.nih.gov/understanding-hiv-aids/glossary/347/immune-system

Cells of the Immune System

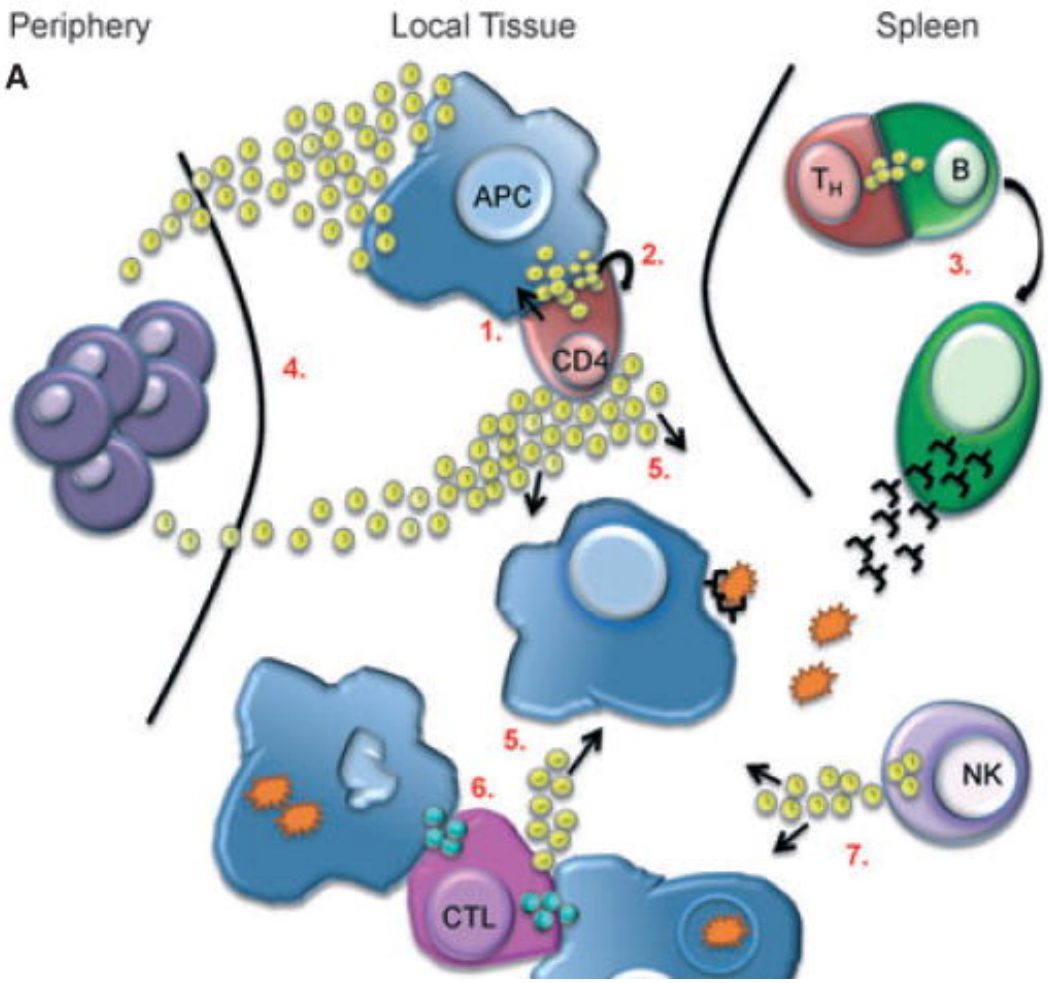


https://www.stemcellimmuneregenerative.com/what-is-the-immune-system



PPAP202000051

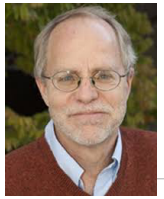
Communication Between Immune Cells



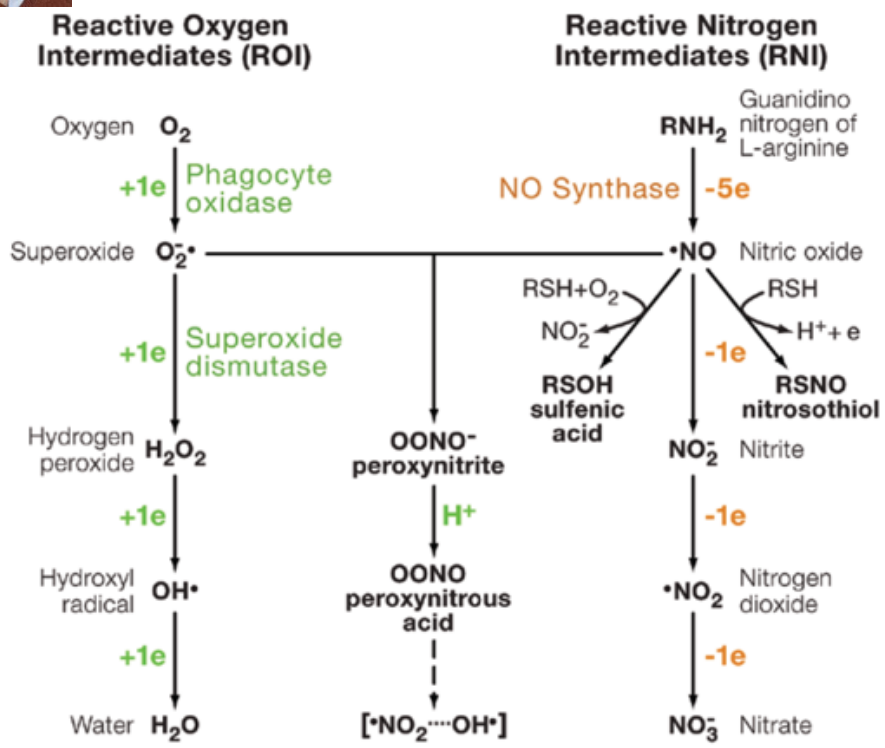
Immunol Rev. 2013 Jan; 251(1): 65–79.

- Direct cell-to-cell contact
- Secreted molecules
  - Cytokines
  - Chemokines
  - RONS
    - Byproducts of cell metabolism
    - Cause cell stress and death
    - Balanced by antioxidants to fine tune RONS concentrations in space and time
    - Low level RONS act as intracellular signaling molecules in steady state and during antigen presentation

RONS of the Immune System



Cellular RONS

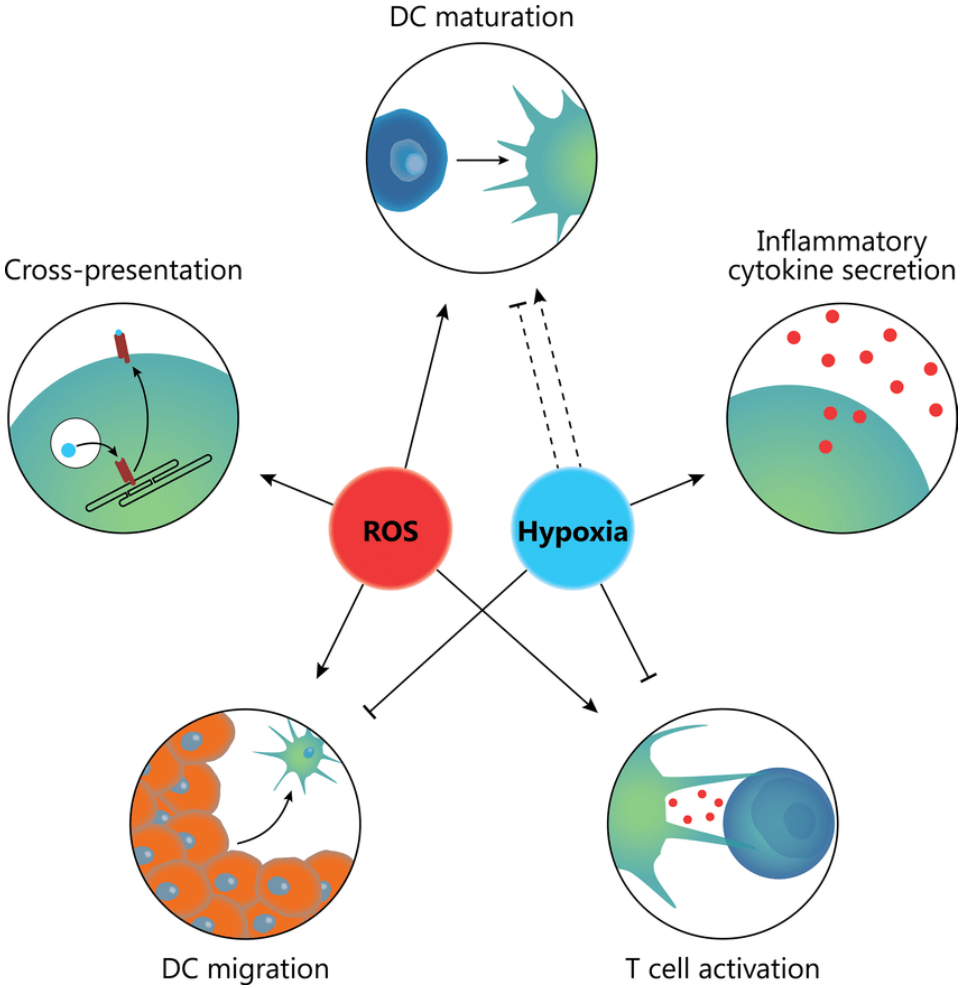


Carl Nathan and Aihao Ding

Plasma RONS

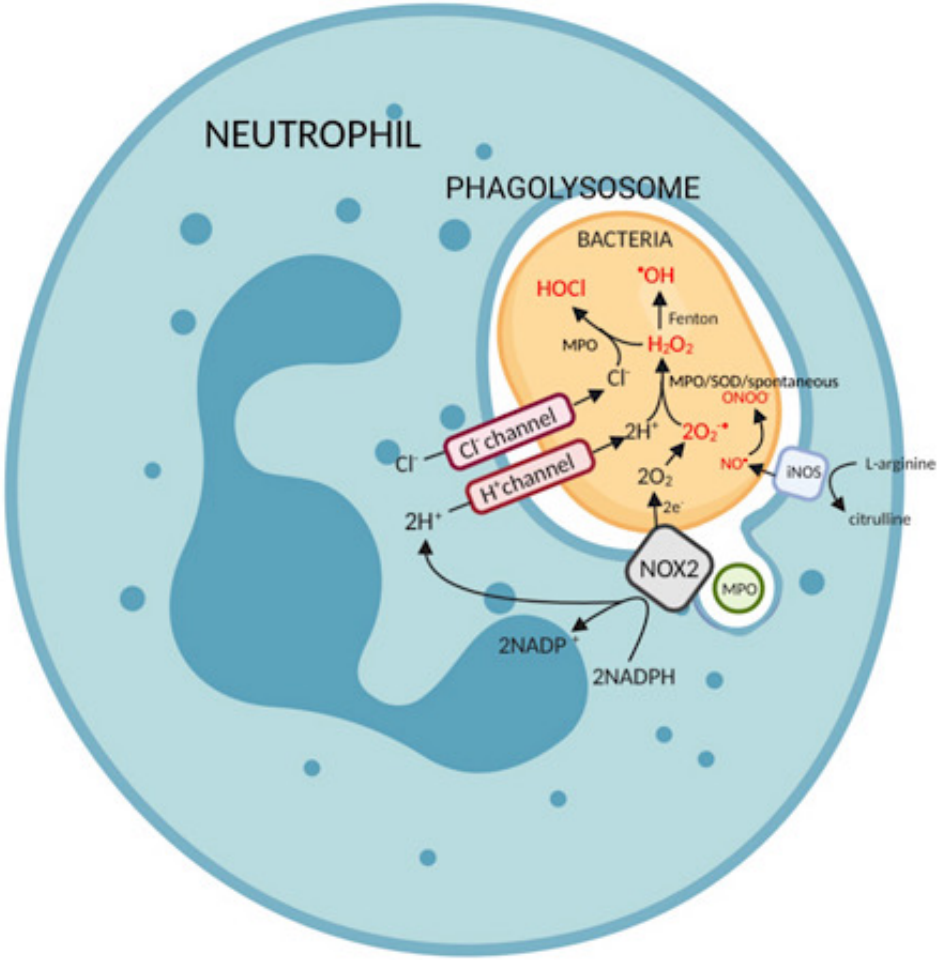
$^{\bullet}O$	Oxygen radical
$^{\bullet}O_2^{-}/^{\bullet}O_2H$	Superoxide/hydroperoxyl radical
H_2O_2	Hydrogen peroxide
$^{\bullet}OH$	Hydroxyl radical
$^1O_2$	Singlet (delta) O_2
O_3	Ozone
$^{\bullet}N$	Nitrogen radical
$^{\bullet}NO$	Nitric oxide radical
$^{\bullet}NO_2$	Nitrogen dioxide radical
NO_2^{-}/HNO_2	Nitrite/nitrous acid
NO_3^{-}/HNO_3	Nitrate/nitric acid
$ONOO^{-}/ONOOH$	Peroxynitrite/peroxynitrous acid
$OCl^{-}/HOCl$	Hypochlorite/hypochlorous acid
O_2NOO^{-}/O_2NOOH	Peroxynitrate/peroxynitric acid

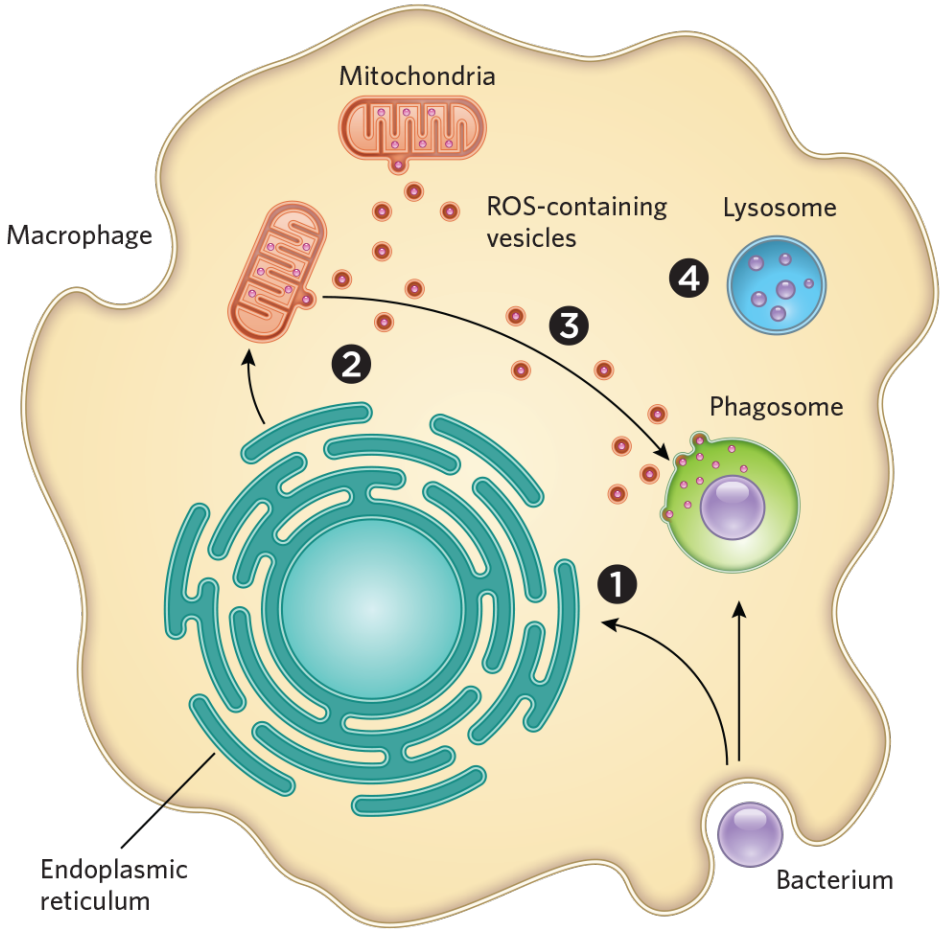
RONS-Mediated Signaling



•Oncotarget 10(8) DOI: 10.18632/oncotarget.26608

Cellular RONS as Effectors





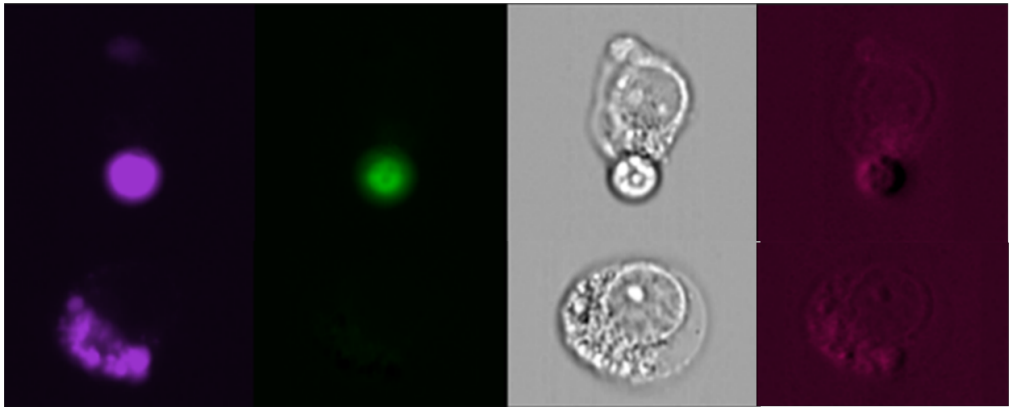
Cell Host & Microbe24, 625–636, November 14, 2018

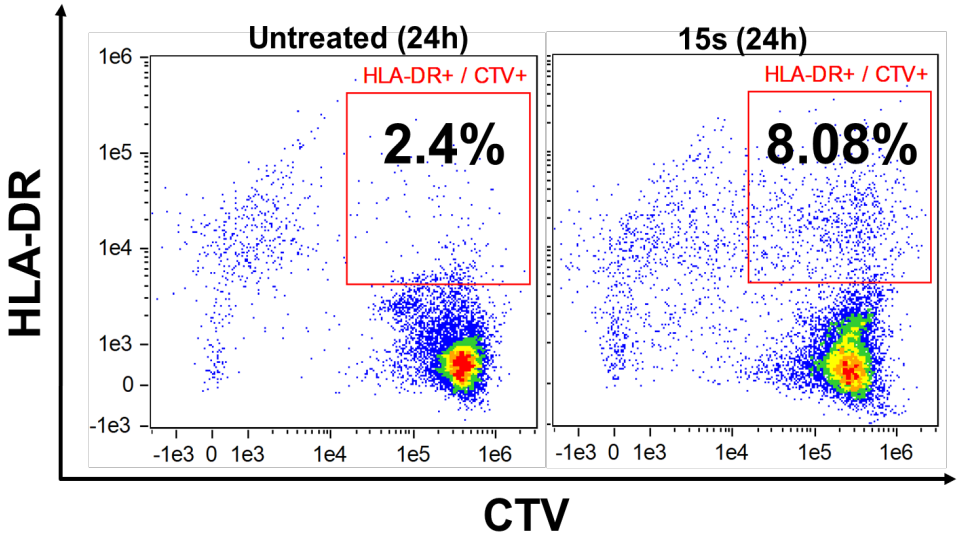
Effects of Plasma on Immune Cells

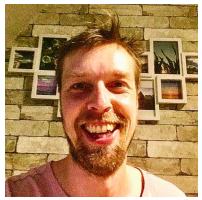
Measurable Immune Cell Functions
1) Recognition and phagocytosis of foreign targets
2) Pathogen killing
3) Cytokine/chemokine secretion
4) Migration
5) Antigen presentation to T and B cells
6) Recruitment of other immune cells
7) Cancer cell killing

Recognition and Phagocytosis of Foreign Targets

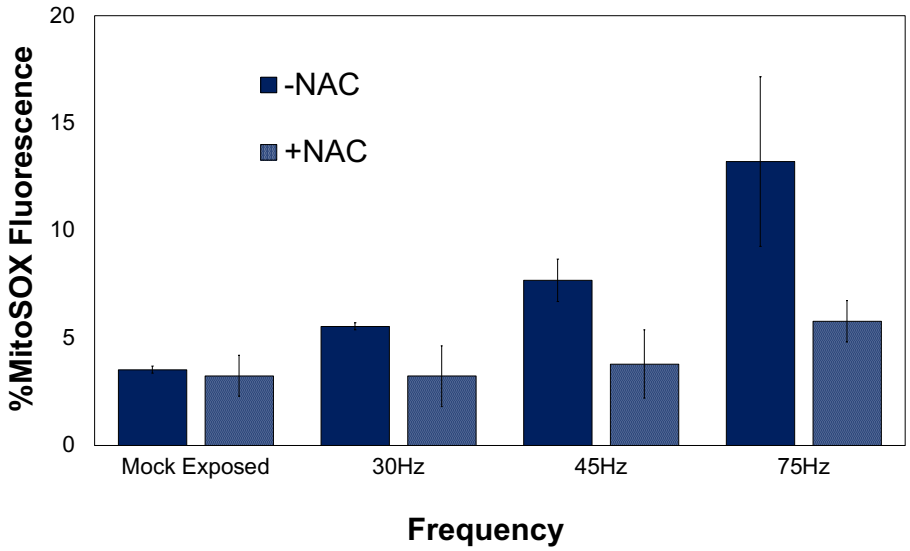
Phagocytosis of 15s NTP treated J-Lat cells (CTV/GFP+)

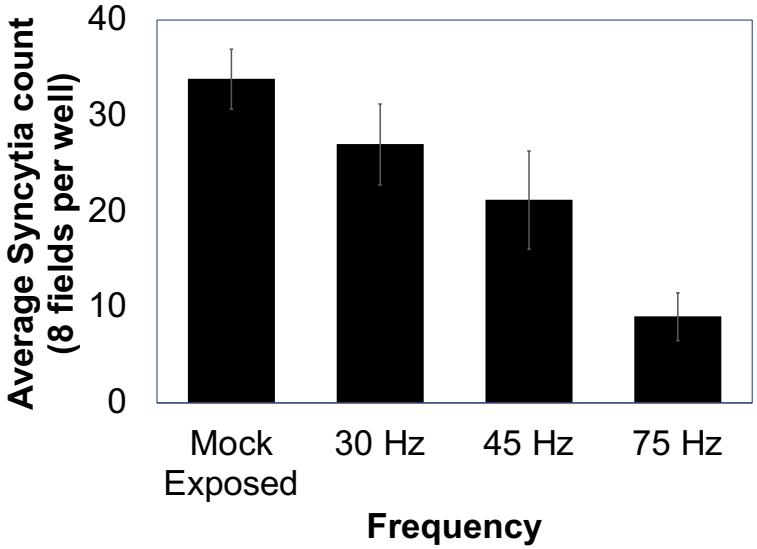


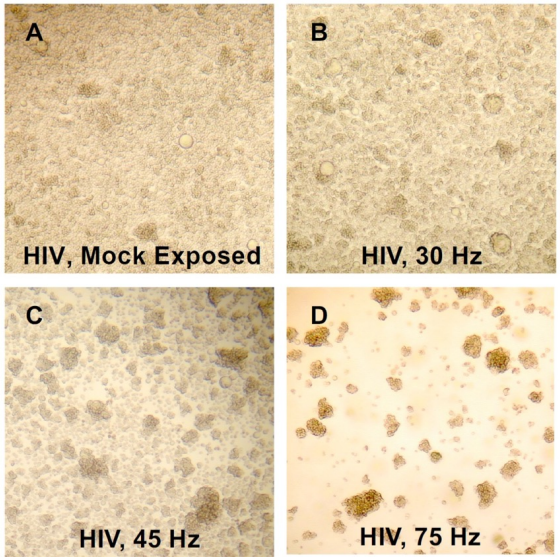




Pathogen Killing – Plasma or Immune?







Pathogen Killing COVID-19

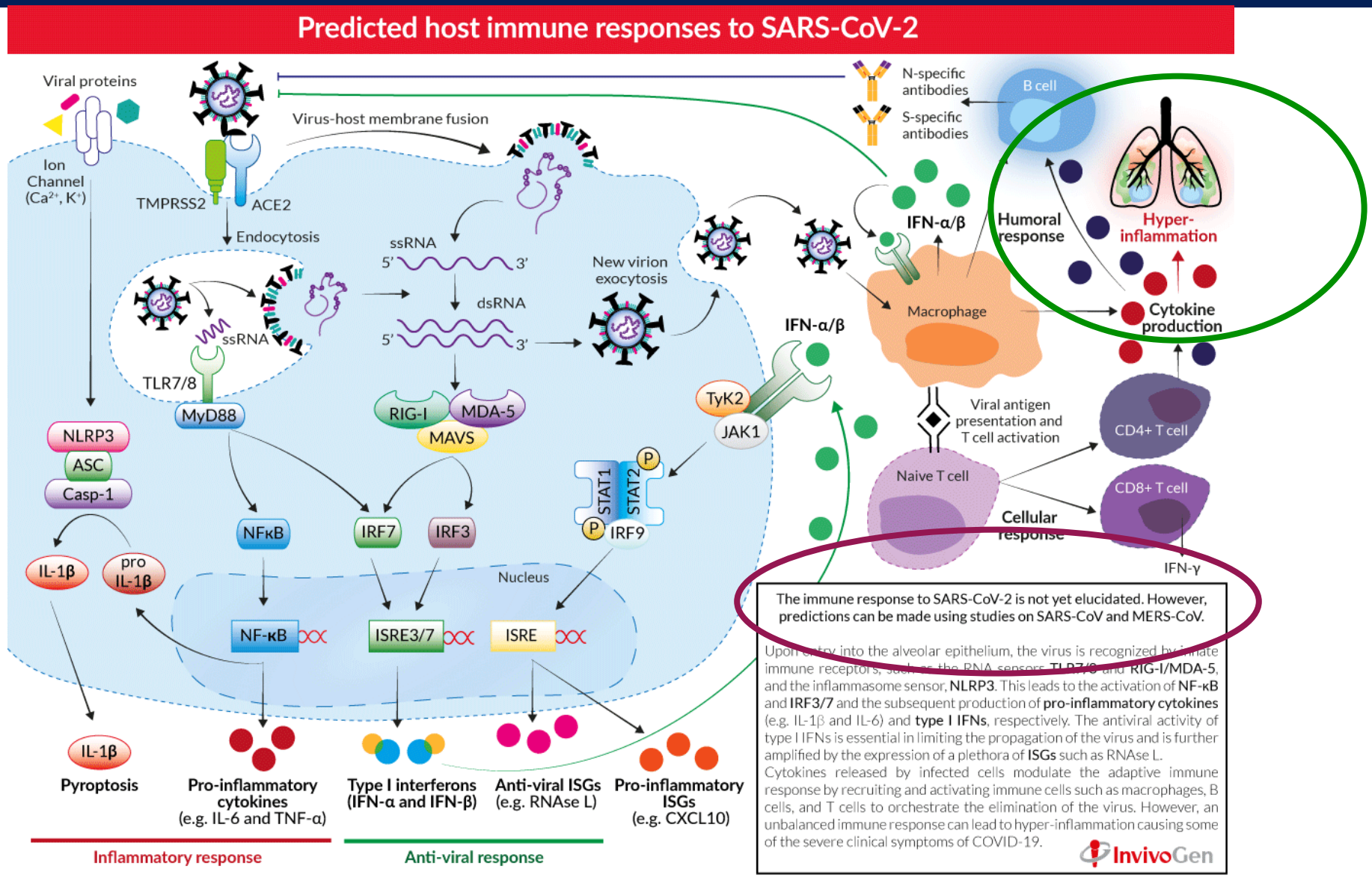
"The initial tests suggest that cold atmospheric plasma kills corona viruses in solution," says Jens Kirsch, CEO of Terraplasma medical.

https://medicalxpress.com/news/2020-06-cold-plasma-coronavirus.html

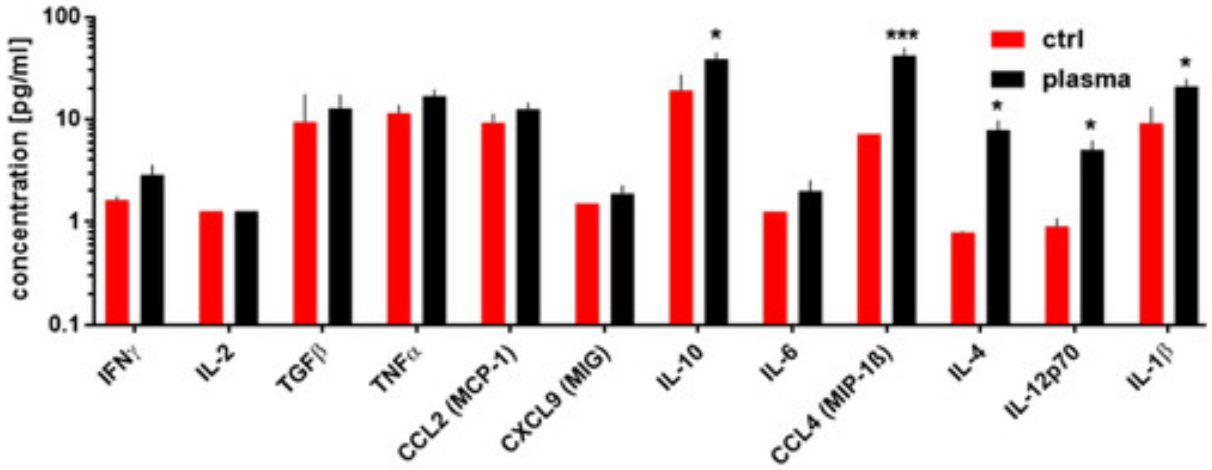
Delivery?
In vivo toxicity of “inhaled” plasma species?

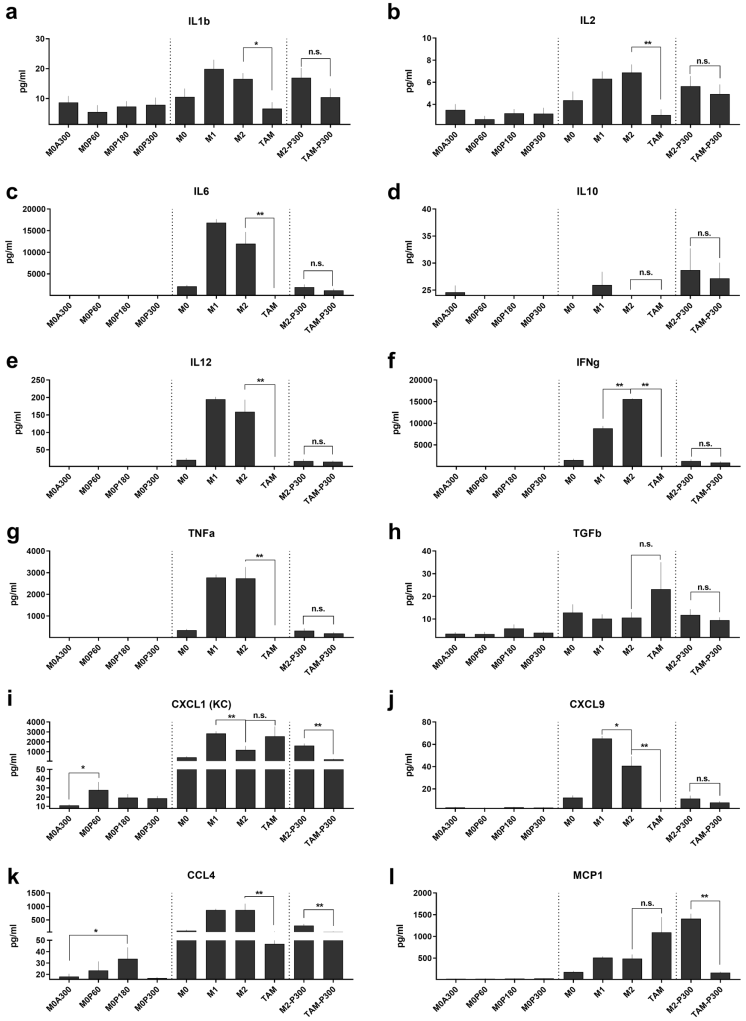
What about the immune system?

Pathogen Killing COVID-19



Cytokine/Chemokine Secretion





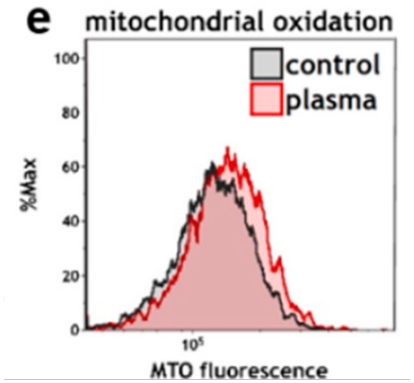
Appl. Sci. **2019**, *9*(4), 660; https://doi.org/10.3390/app9040660

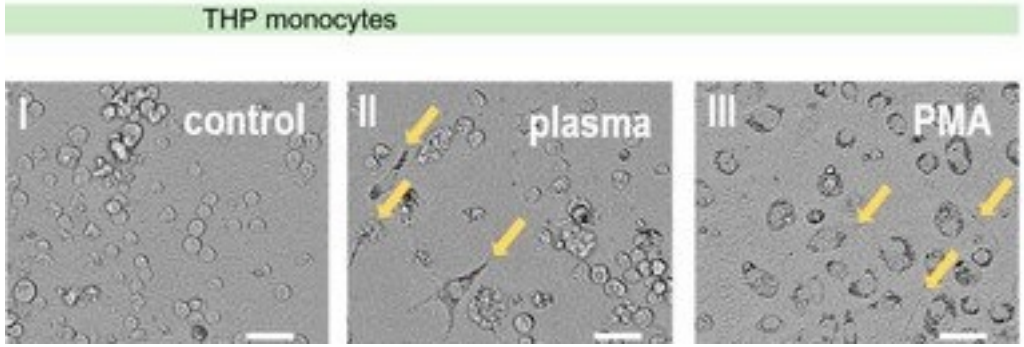
Clinical Plasma Medicine, Volume 11, September 2018, Pages 1-9

Maturation/Migration of Monocytic Cells

Mitochondrial ROS enhance monocytic maturation and migration

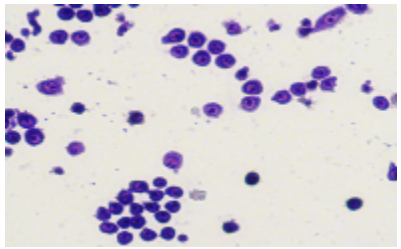
Cell Metabolism, Volume 18, Issue 2, 6 August 2013, Pages 265-278



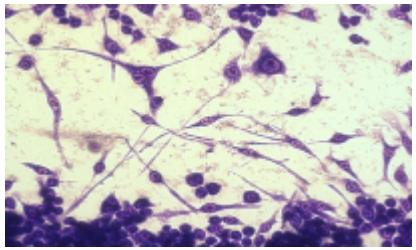


Appl. Sci. **2019**, *9*(12), 2530; https://doi.org/10.3390/app9122530

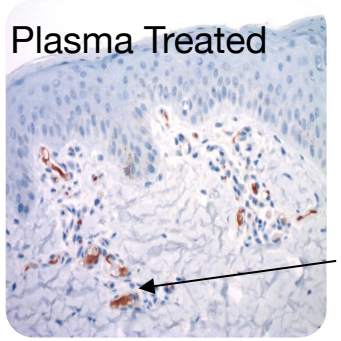
Untreated



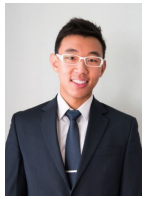
141mJ: 15Hz



doi/10.1002/ppap.201400168

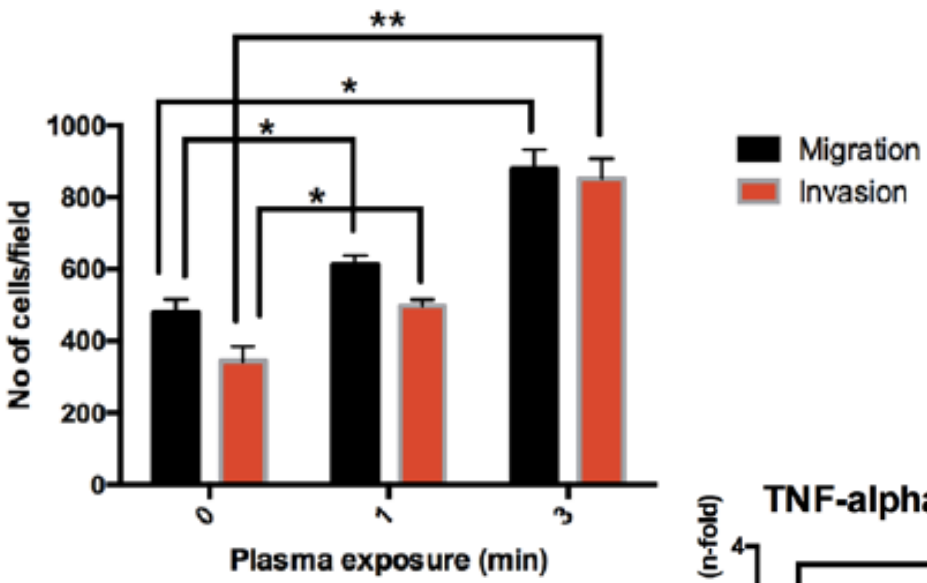


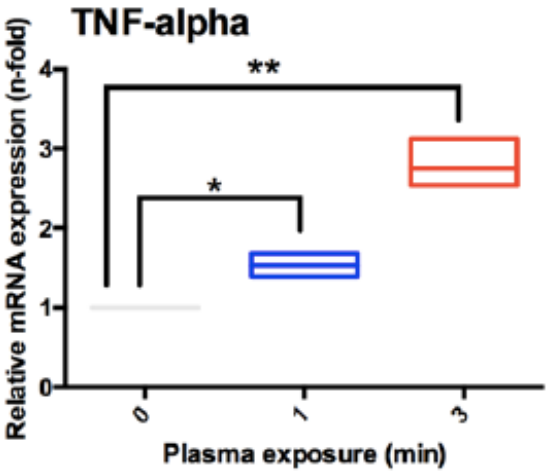
APC (CD163)

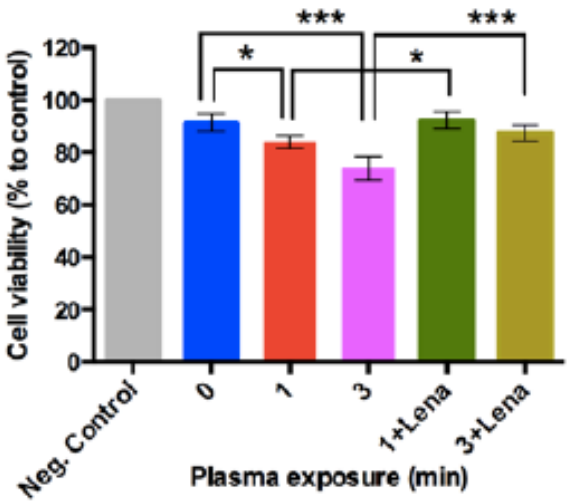


Plasma Medicine: 10.1615/PlasmaMed.2017019883

Cancer Cell Killing





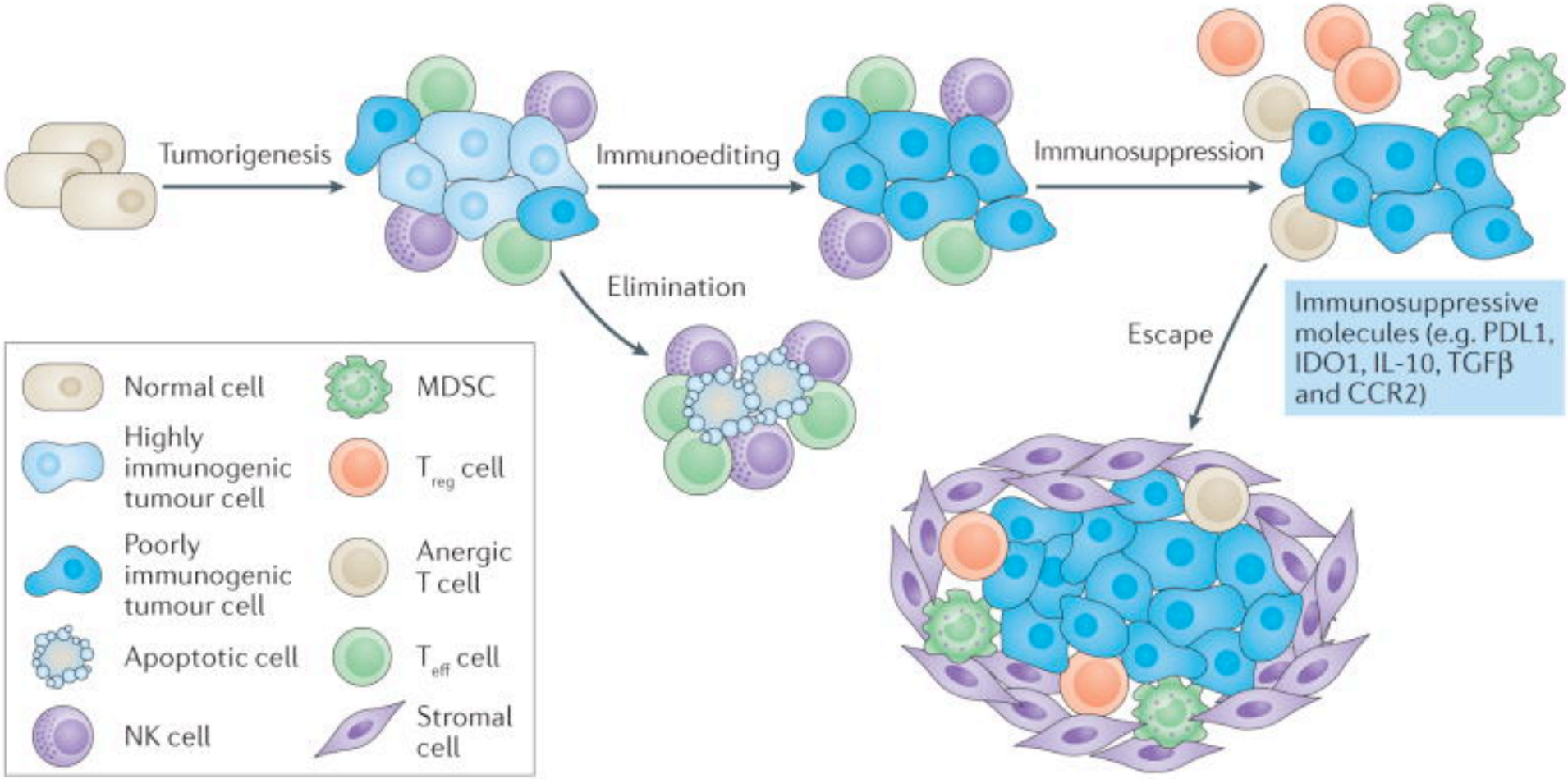


J. Phys. D: Appl. Phys. **49** (2016) 084001

Indirect Effect of Plasma on Immune Cells

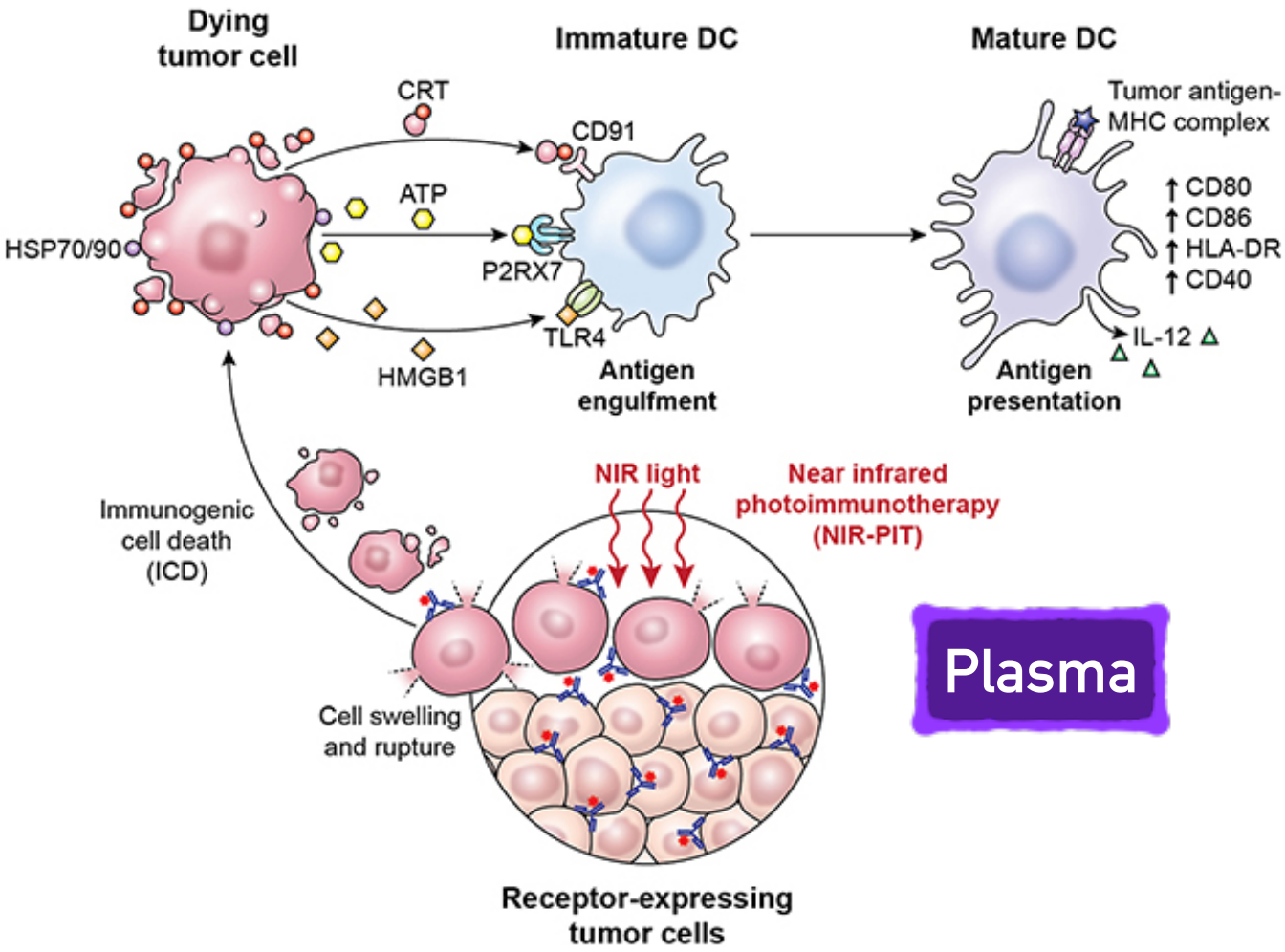
- More practical approach because immune cells are not easily accessible
- Evidence from studies in **cancer treatment** and **wound healing** that diseased cells can be triggered to signal to immune cells and recruit their help

Cancer



Nat Rev Cancer. 2017

Immunogenic Cell Death



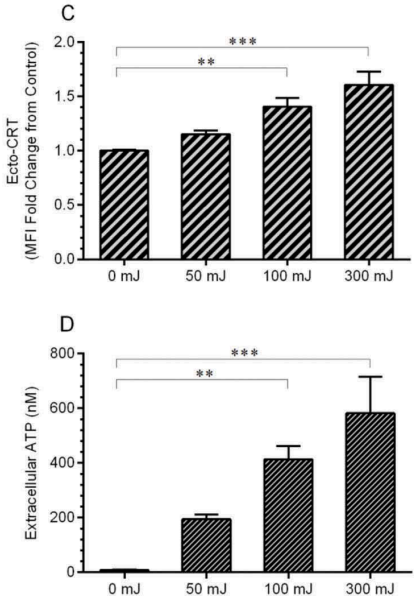
Plasma

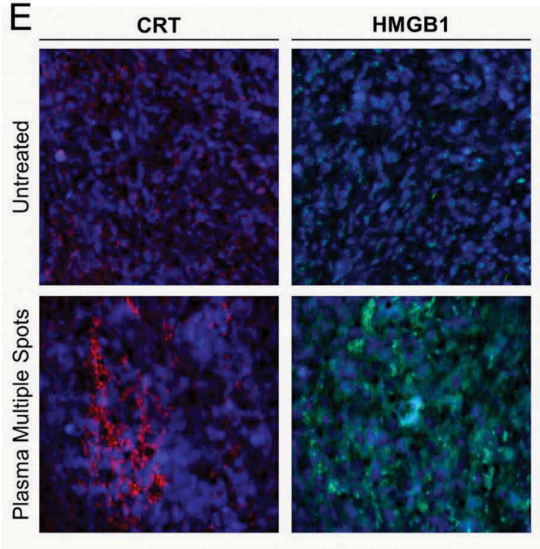
Oncotarget. 2017; 8:10425-10436

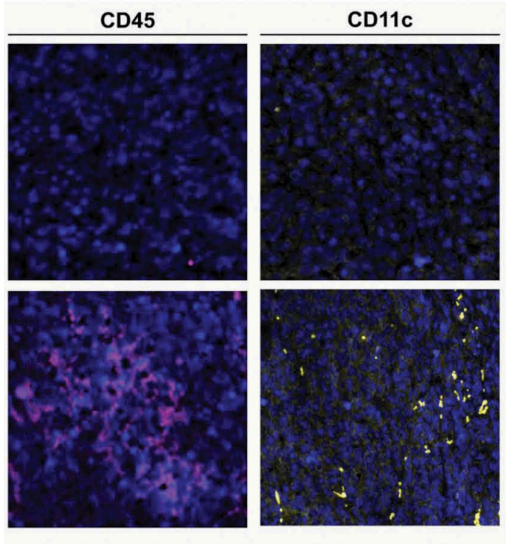
DOI: https://doi.org/10.1038/mt.2

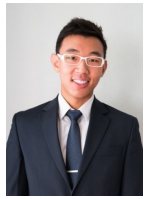
Indirect Effect of Plasma on Immune Cells

Induction of immunogenic cell death

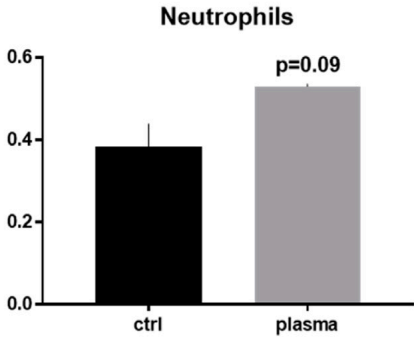


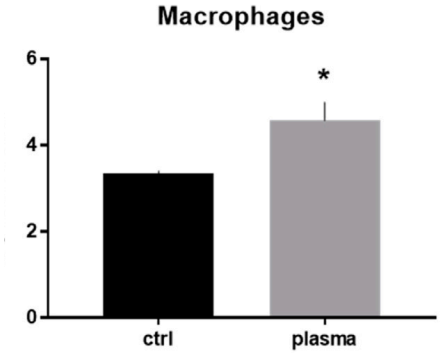






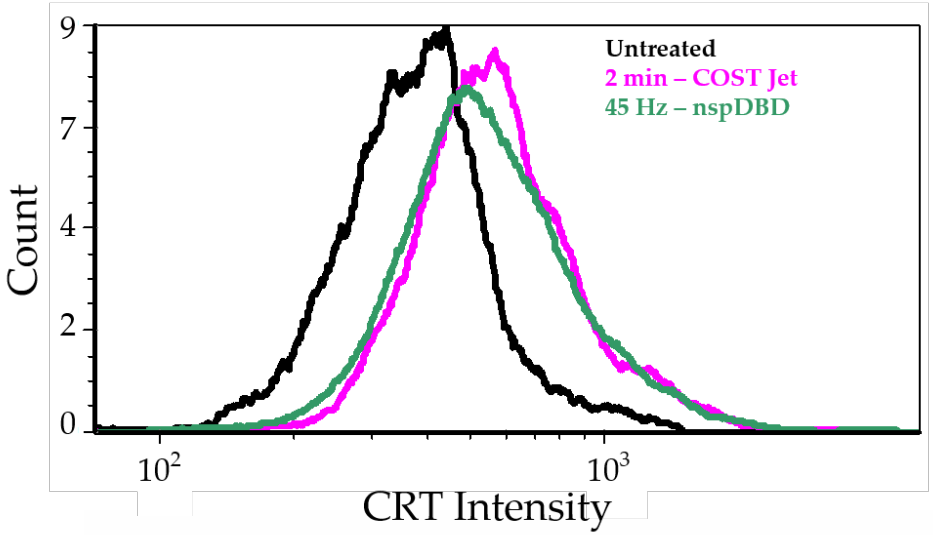
ONCOIMMUNOLOGY 2018, VOL. 7, NO

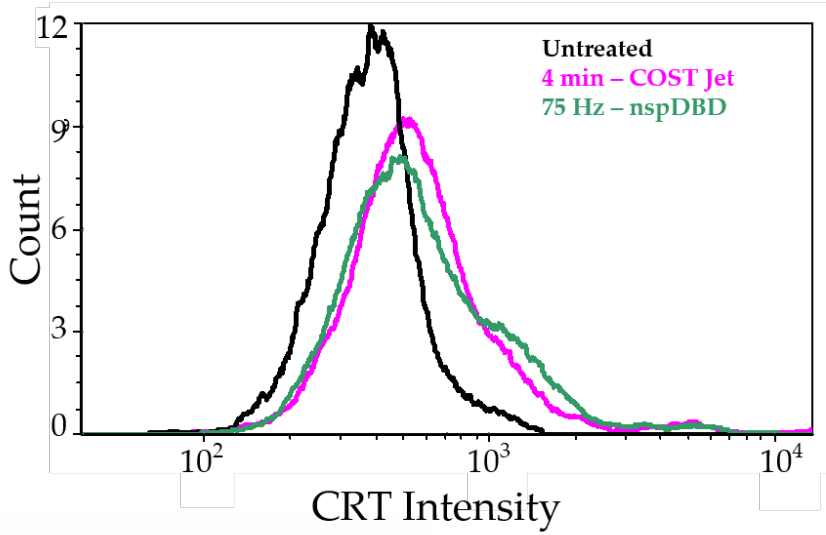


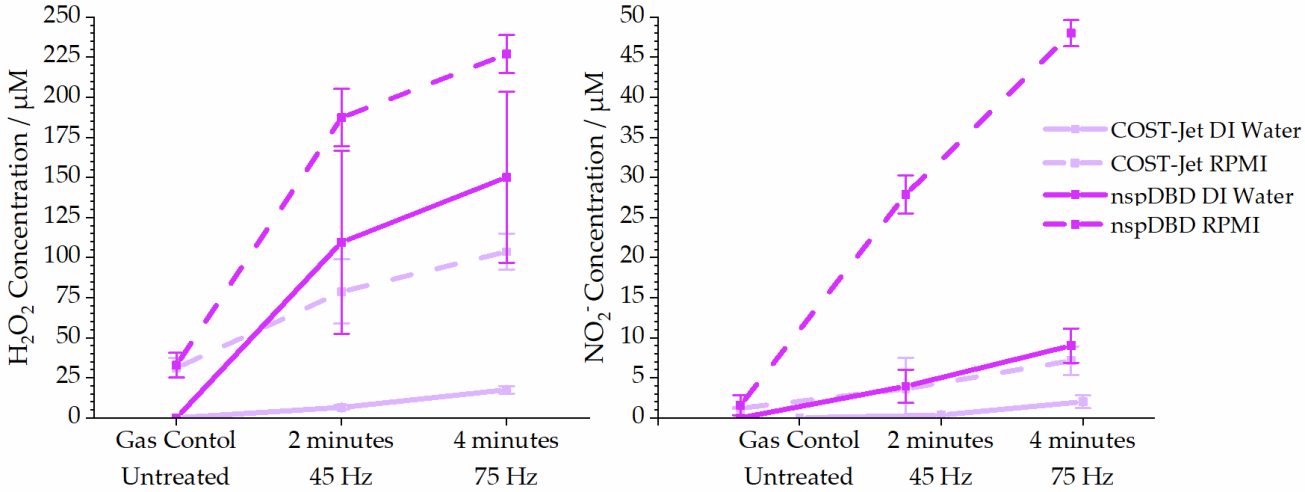


Clinical Plasma Medicine 11 (2018) 10–17

Active Plasma Species?

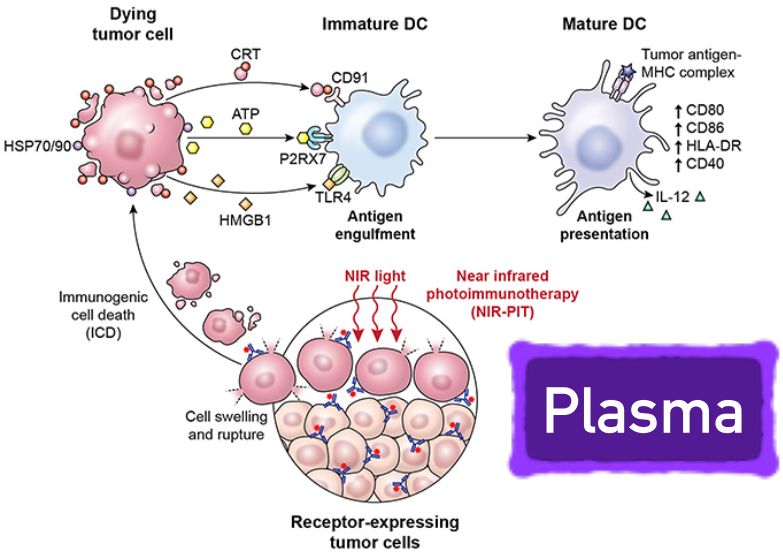






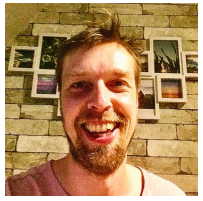
Appl. Sci. **2020**, *10*(6), 2025; https://doi.org/10.3390/app10062025

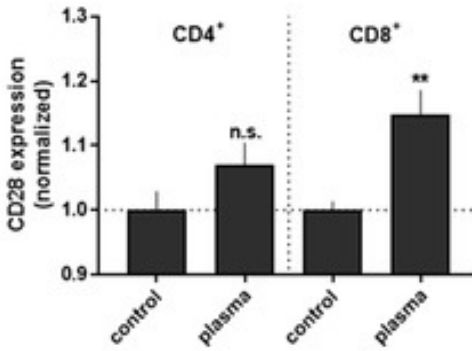
Enhanced Antigen Presentation?



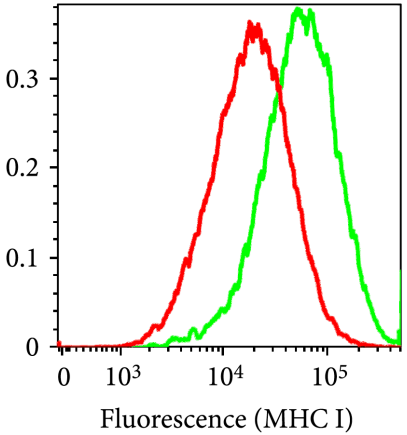
Plasma

Oncotarget. 2017; 8:10425-10436





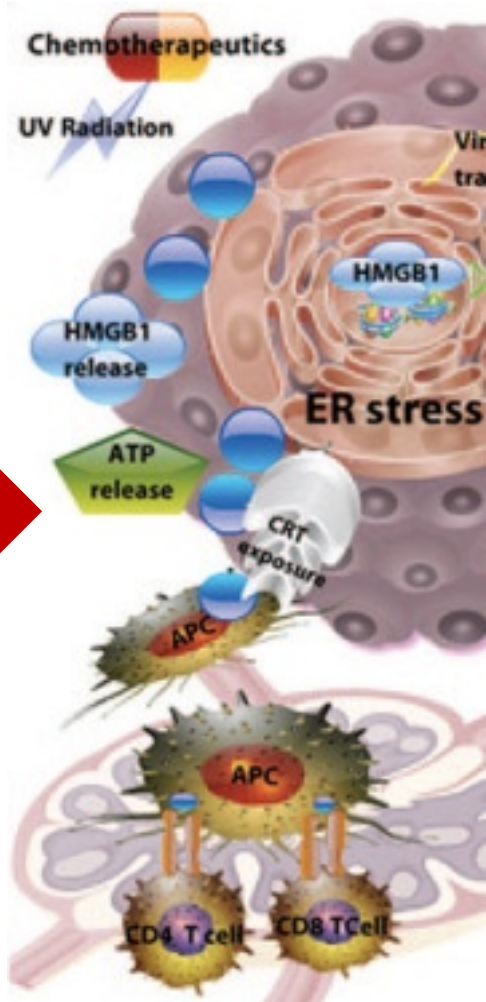
Appl. Sci. **2019**, *9*(4), 660; https://doi.org/10.3390/app9040660



0 control

120 plasma

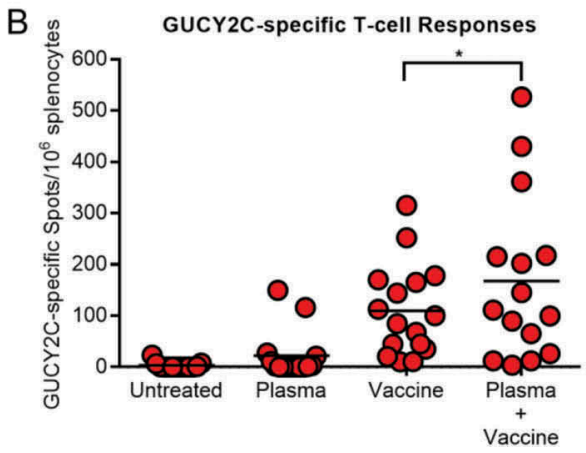
Oxidative Medicine and Cellular Longevity https://doi.org/10.1155/2017/4396467

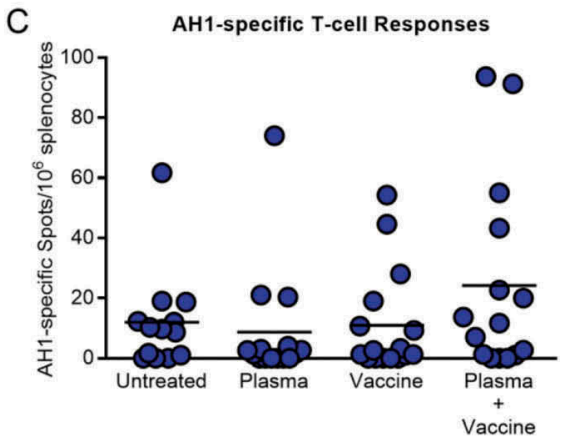


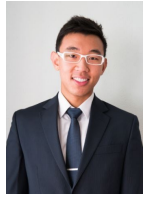
DOI:https://doi.org/10.1038/mt.2013.220

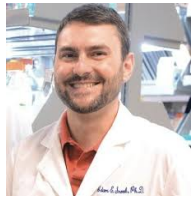
Indirect Effect of Plasma on Immune Cells

Development of protective adaptive responses

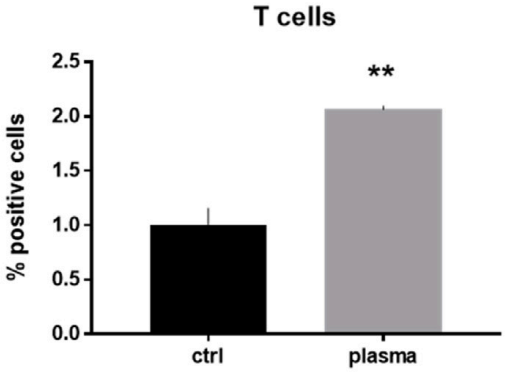




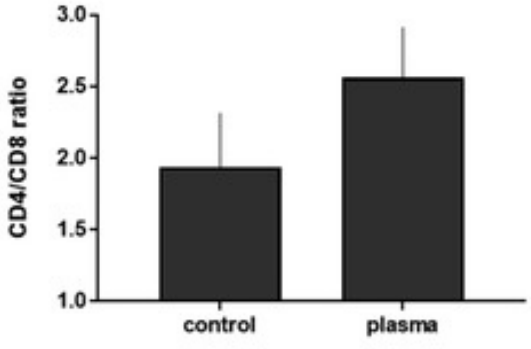




ONCOIMMUNOLOGY 2018, VOL. 7, NO. 9, e1484978



Clinical Plasma Medicine 11 (2018) 10–17



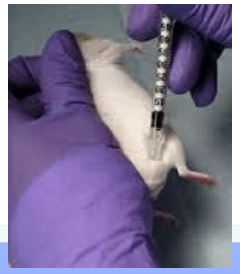
Appl. Sci. **2019**, *9*(4), 660; https://doi.org/10.3390/app9040660

Indirect Effect of Plasma on Immune Cells

Development of memory

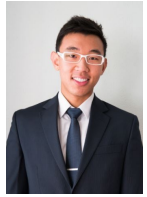
In vitro ICD

Immunize Animals

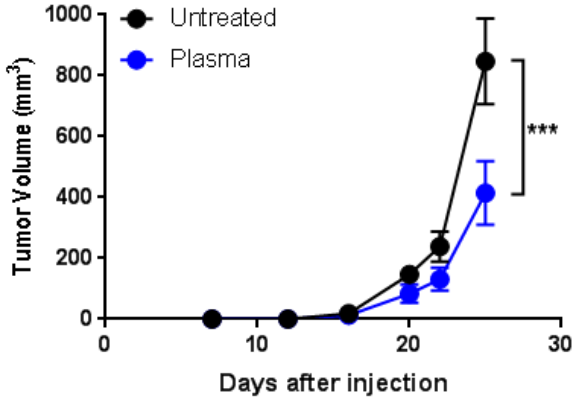


Challenge

Tumor growth



	Mice with tumors < 850 mm^3	Mice without tumors
Media	40%	0%
Cisplatin	40%	10%
Plasma	90%	30%



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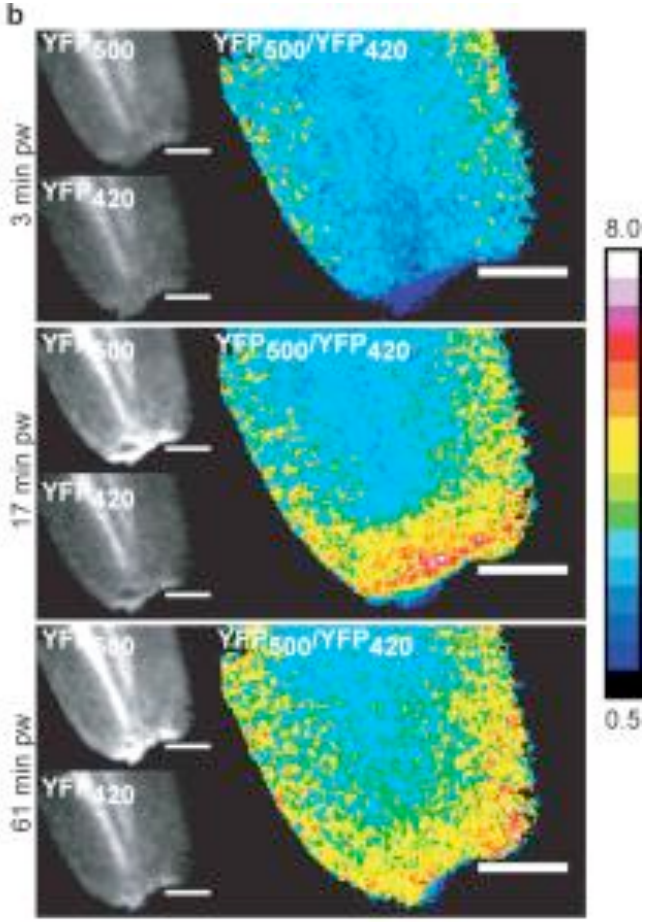
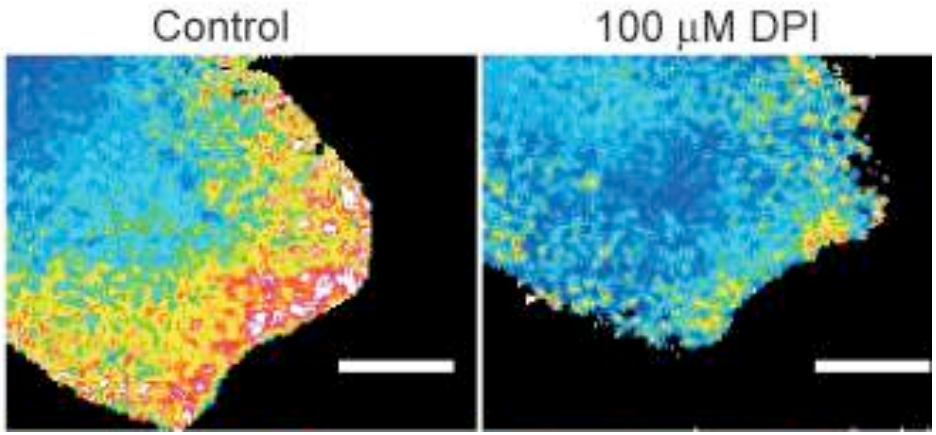
RONS in Wound Healing

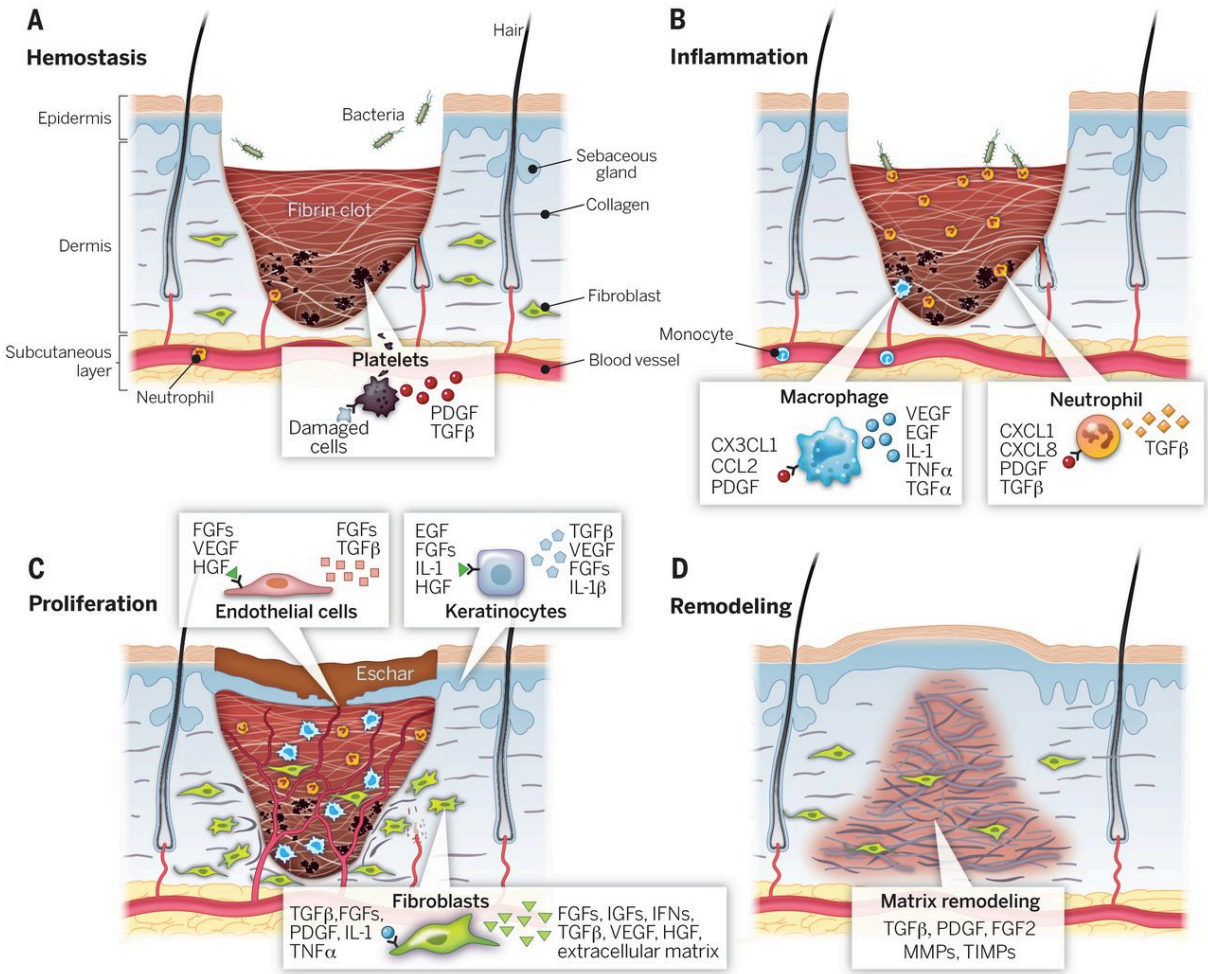




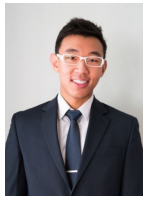
H_2O_2 concentration at the wound margin, starting ~3 min after wounding and peaking at ~20 min and this gradient is required for rapid recruitment of leukocytes to the wound

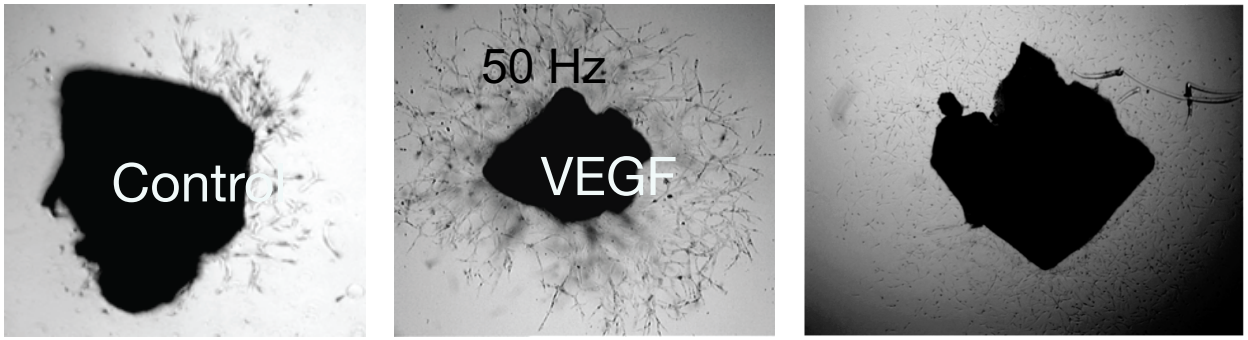
Nature. 2009 Jun 18; 459(7249): 996–999.

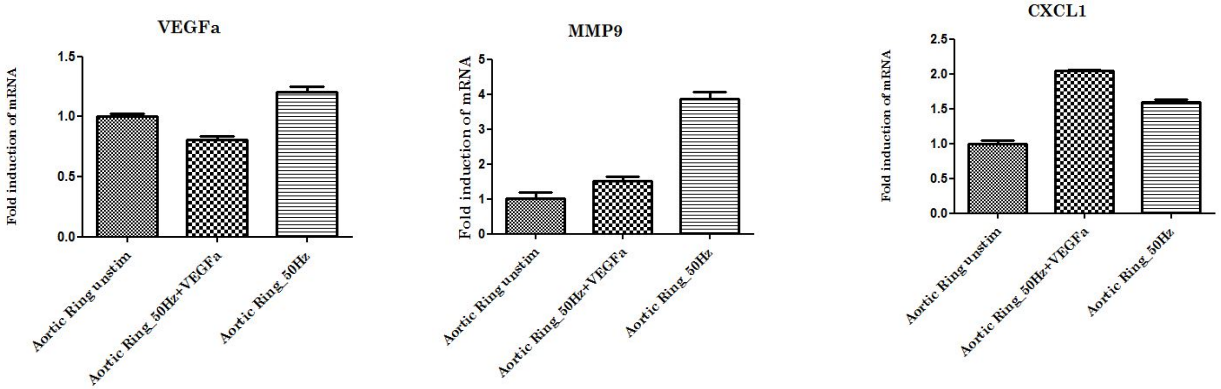
Immune Function in Wound Healing



Plasma Triggers Immune Mediators of Wound Healing





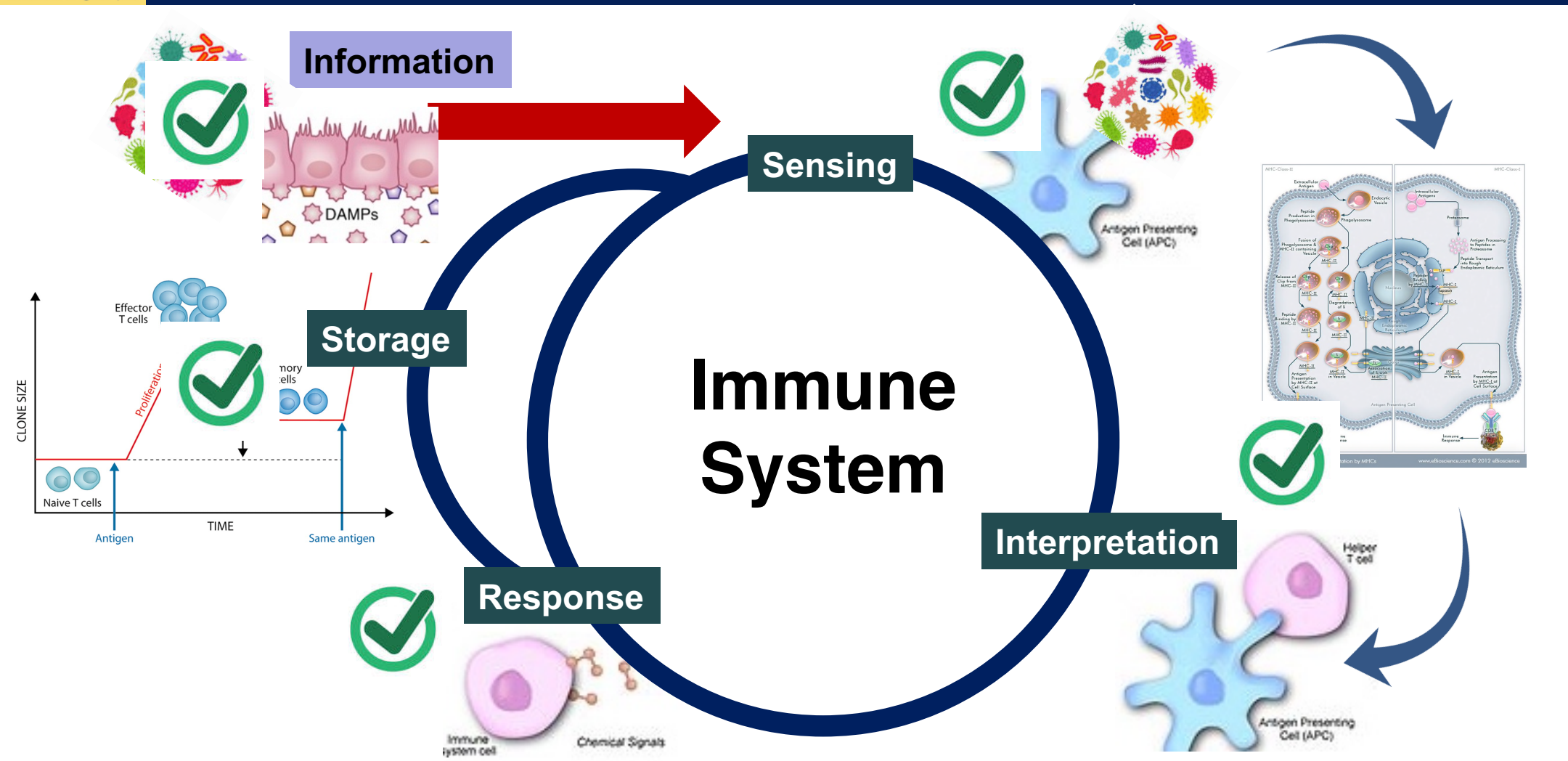


Dec 2015 · Physics of Plasmas, DOI: 10.1063/1.4933403

Effects of Plasma on Immune Cells

Measurable Immune Cell Functions	
1) Recognition and phagocytosis of foreign targets	✓
2) Pathogen killing	?
3) Cytokine/chemokine secretion	✓
4) Migration	✓
5) Antigen presentation to T and B cells	✓ ?
6) Recruitment of other immune cells	?
7) Cancer cell killing	✓

Immune System – Information Management



Adapted from: doi: 10.3389/fimmu.2016.00125, doi.org/10.1681/ASN.2007020151