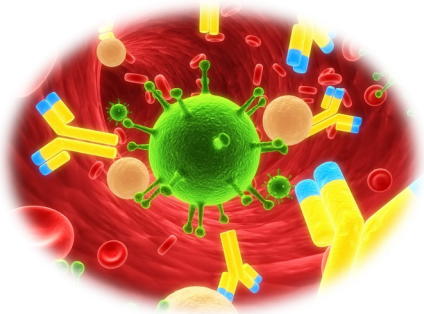
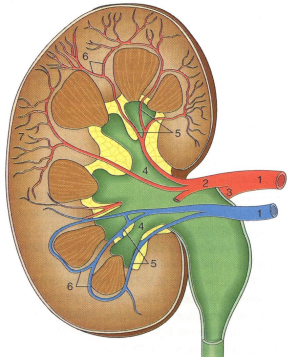
APCN x TSN 2025
23rd Asian Pacific Congress of Nephrology
長庚醫療財團法人
Chang Gung Medical Foundation





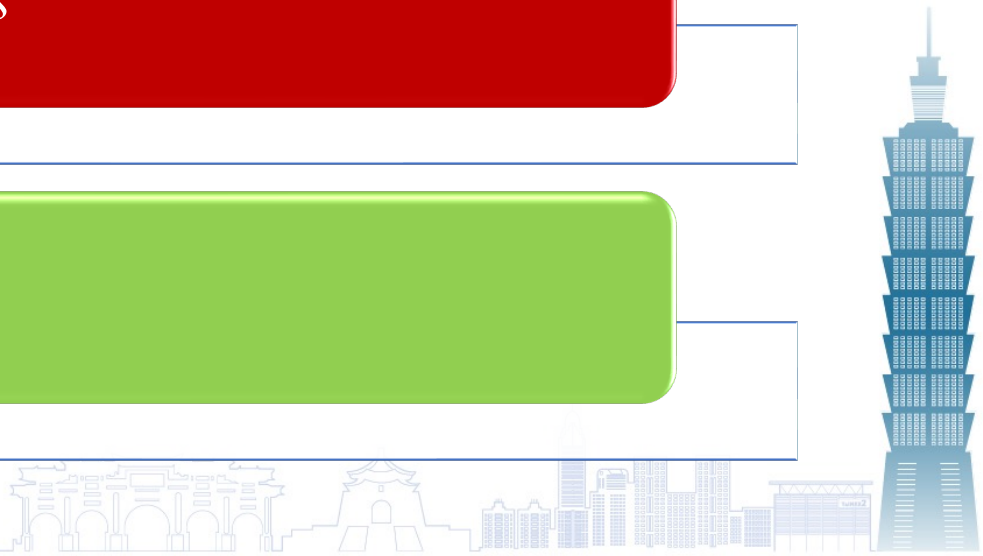
Immunometabolic Reprogramming as a Next-Gen Strategy for Lupus Nephritis

Huang-Yu Yang
Department of Nephrology, Chang Gung Memorial Hospital
, School of Medicine, Chang Gung University

Immunometabolims

Micromanaging lupus nephritis

Glutamine and kidney disease



APCN x TSN 2025
23rd Asian Pacific Congress of Nephrology

You are what you eat!

食肉者勇敢而捍，Carnivores are brave and fierce

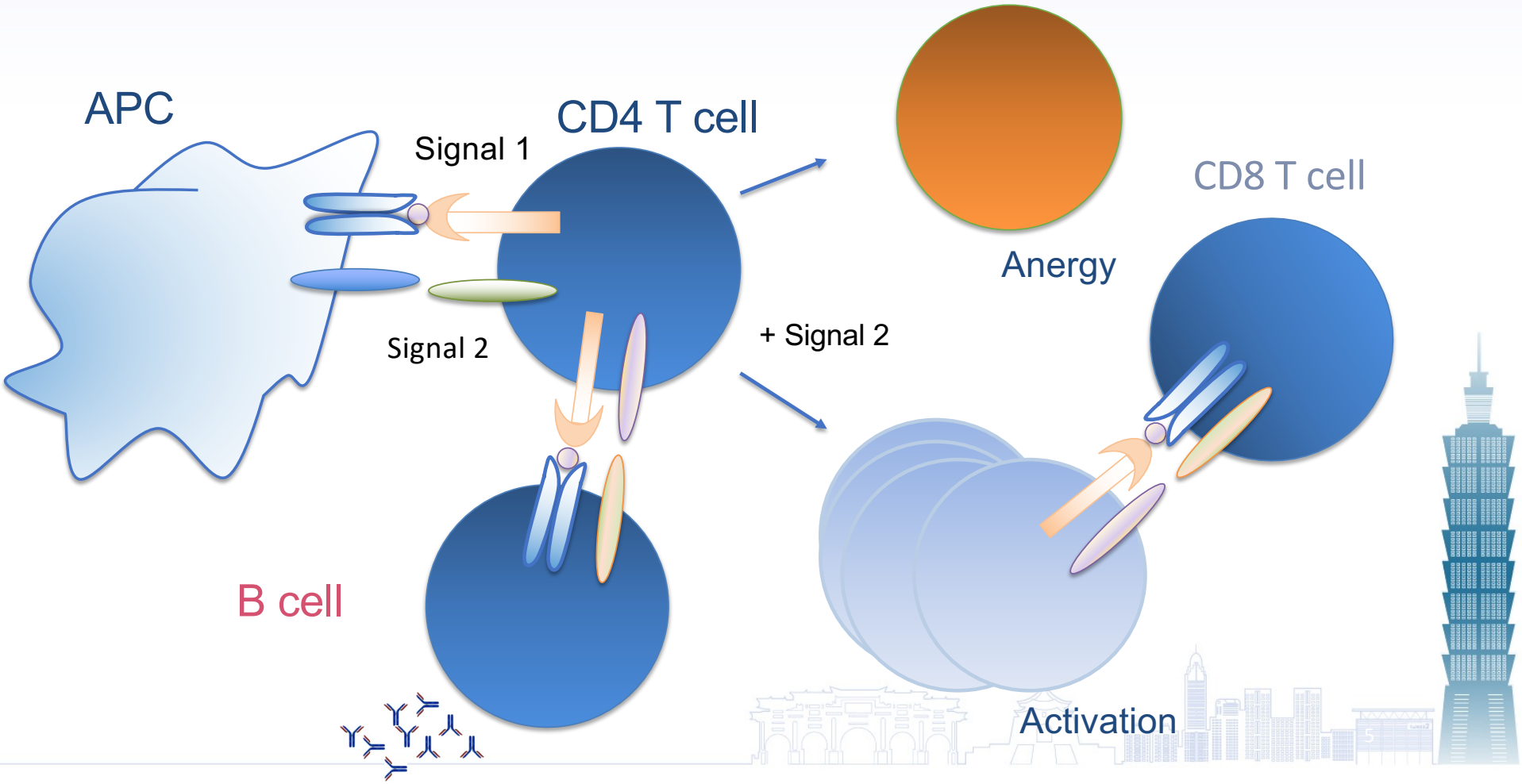
食穀者智惠而巧，Grain eaters are wise and skillful

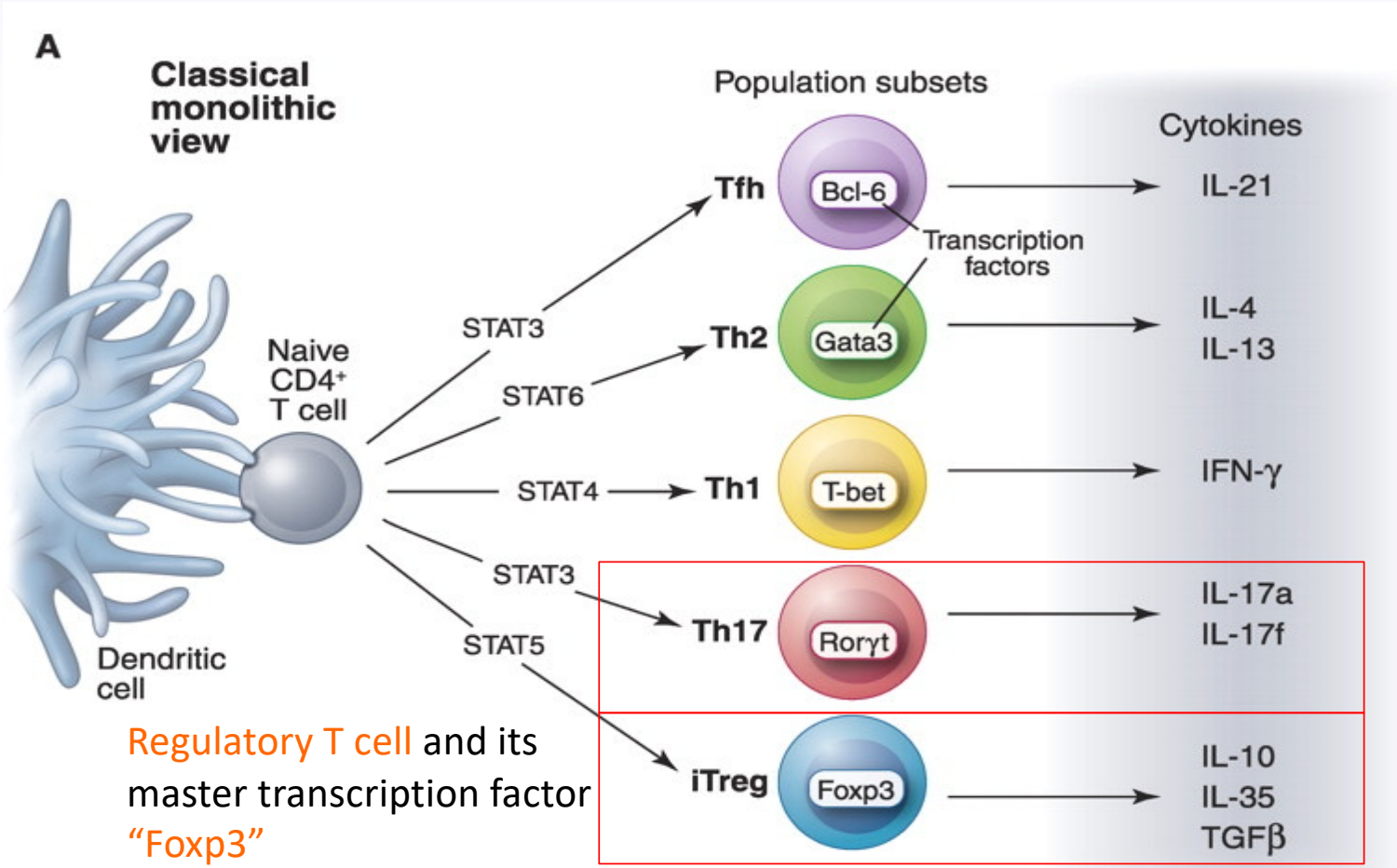
食氣者神明而壽，Those who eat breath will be enlightened and live longer

不食者不死而神。He who does not eat will never die and become a god

《大戴禮記·易本命》

CD4 T Cell activation

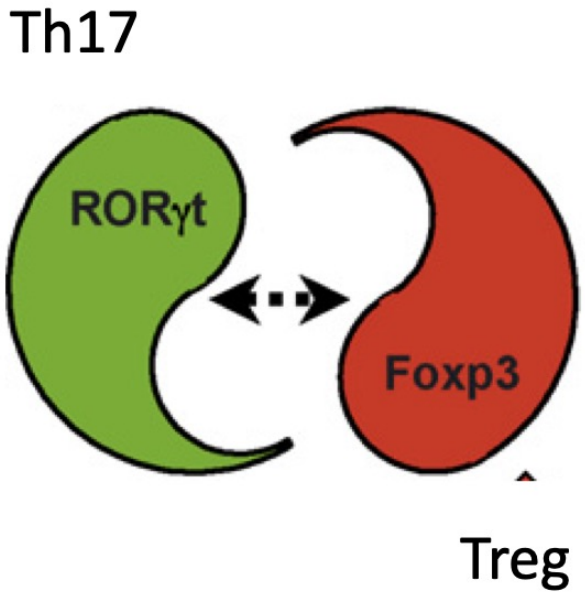


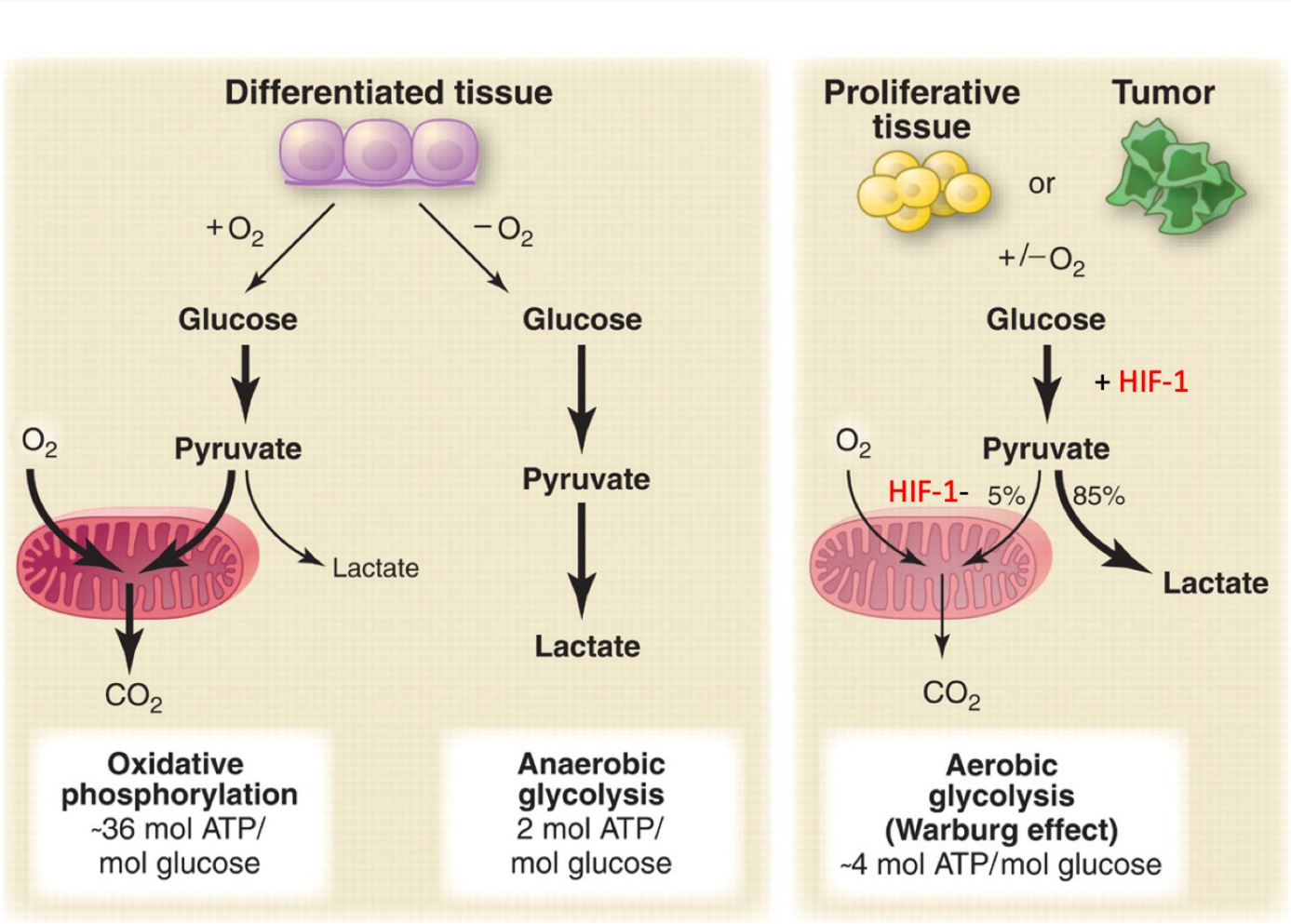


Regulatory T cell and its master transcription factor "Foxp3"

John J. O'Shea, and William E. Paul Science 2010;327:1098-1102

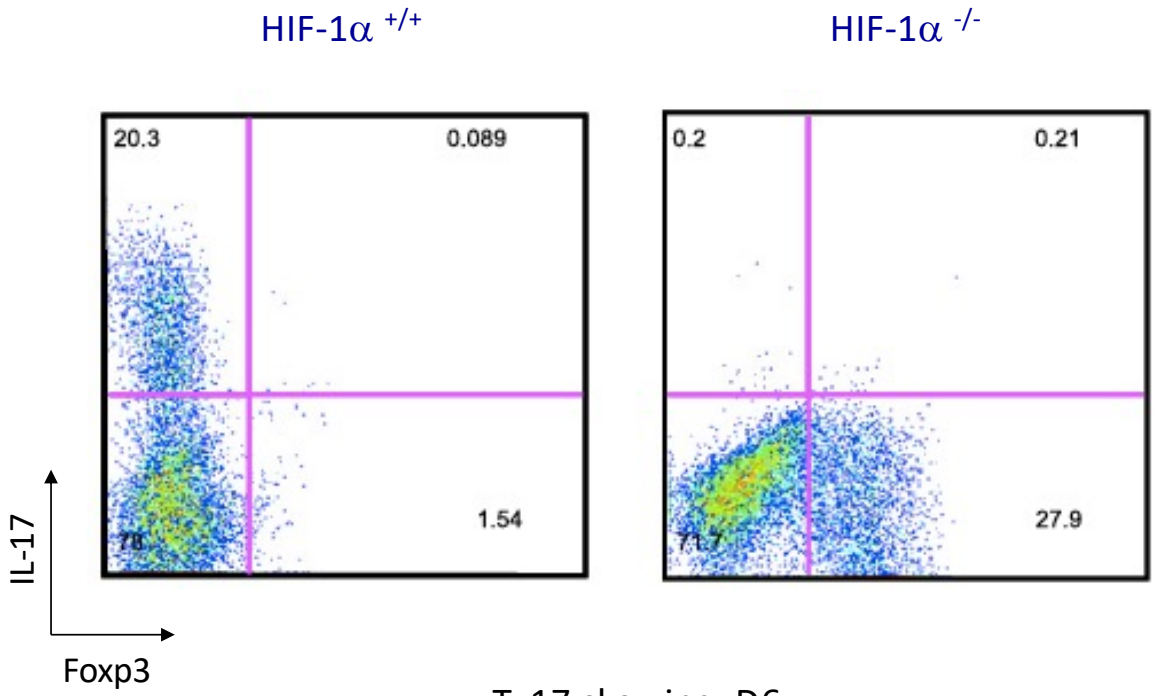
Background-Treg/Th17 cells



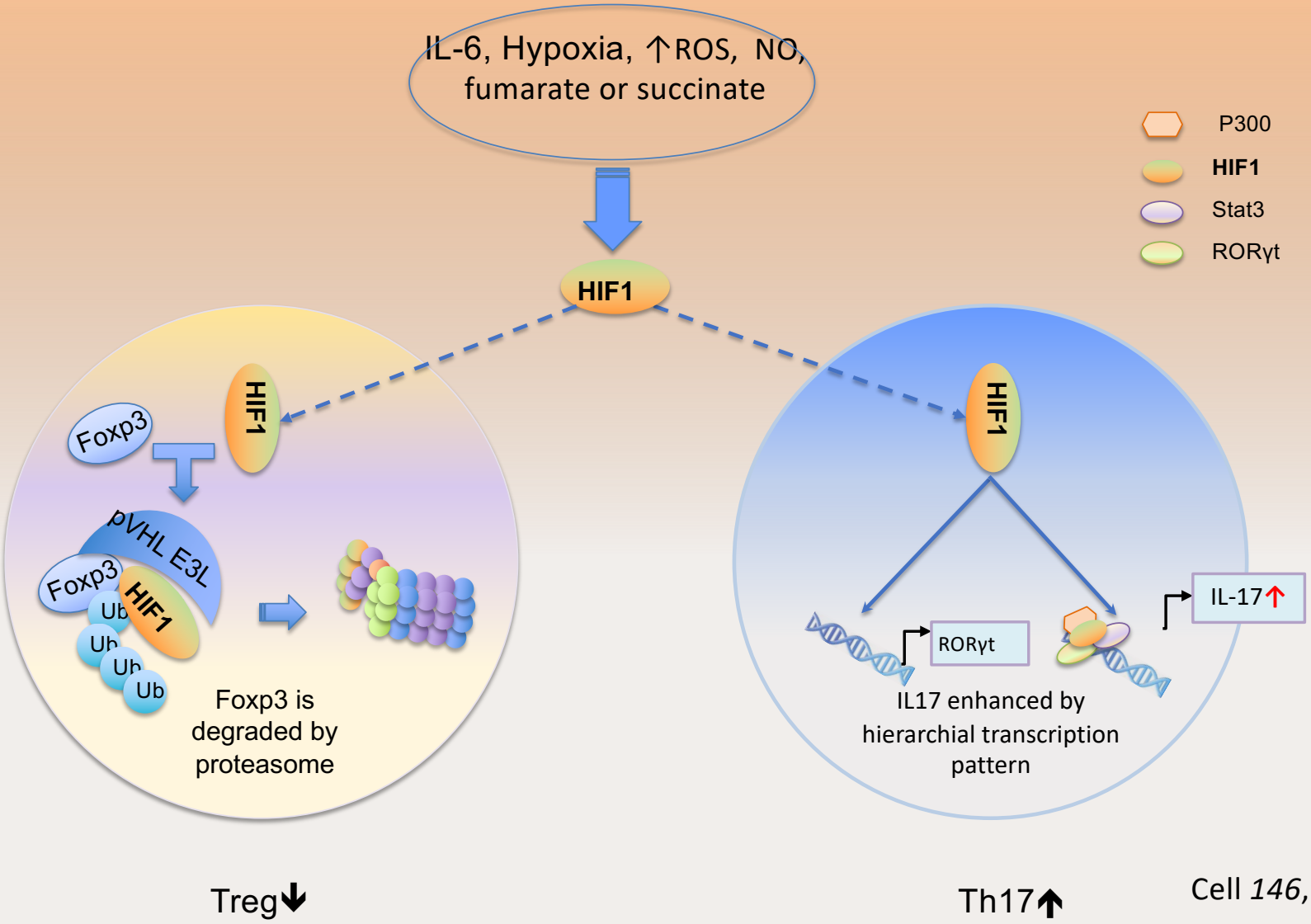


Science 22 May 2009:
Vol. 324 no. 5930 pp. 1029-1033

HIF-1a is required for T_H17 development and related to decreased Treg



T_H17 skewing, D6

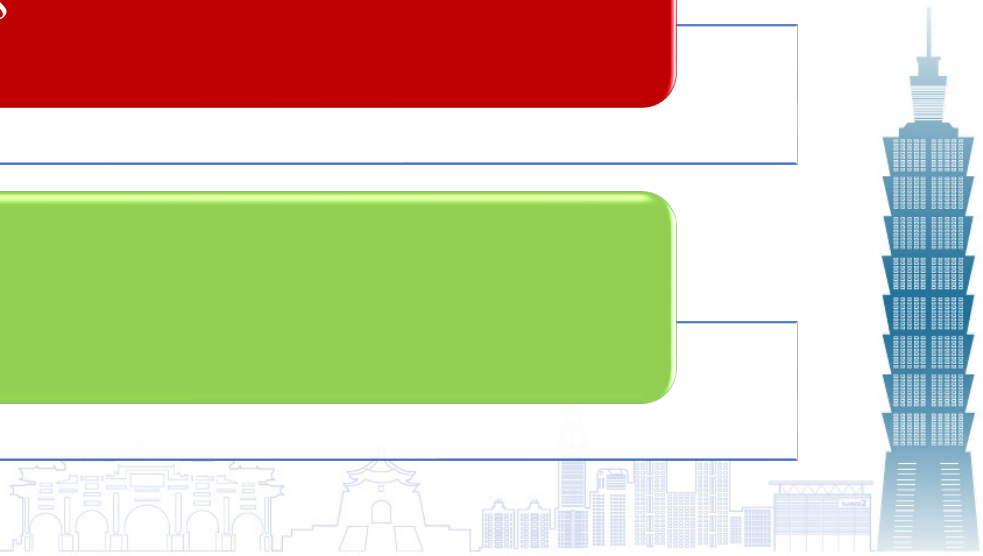


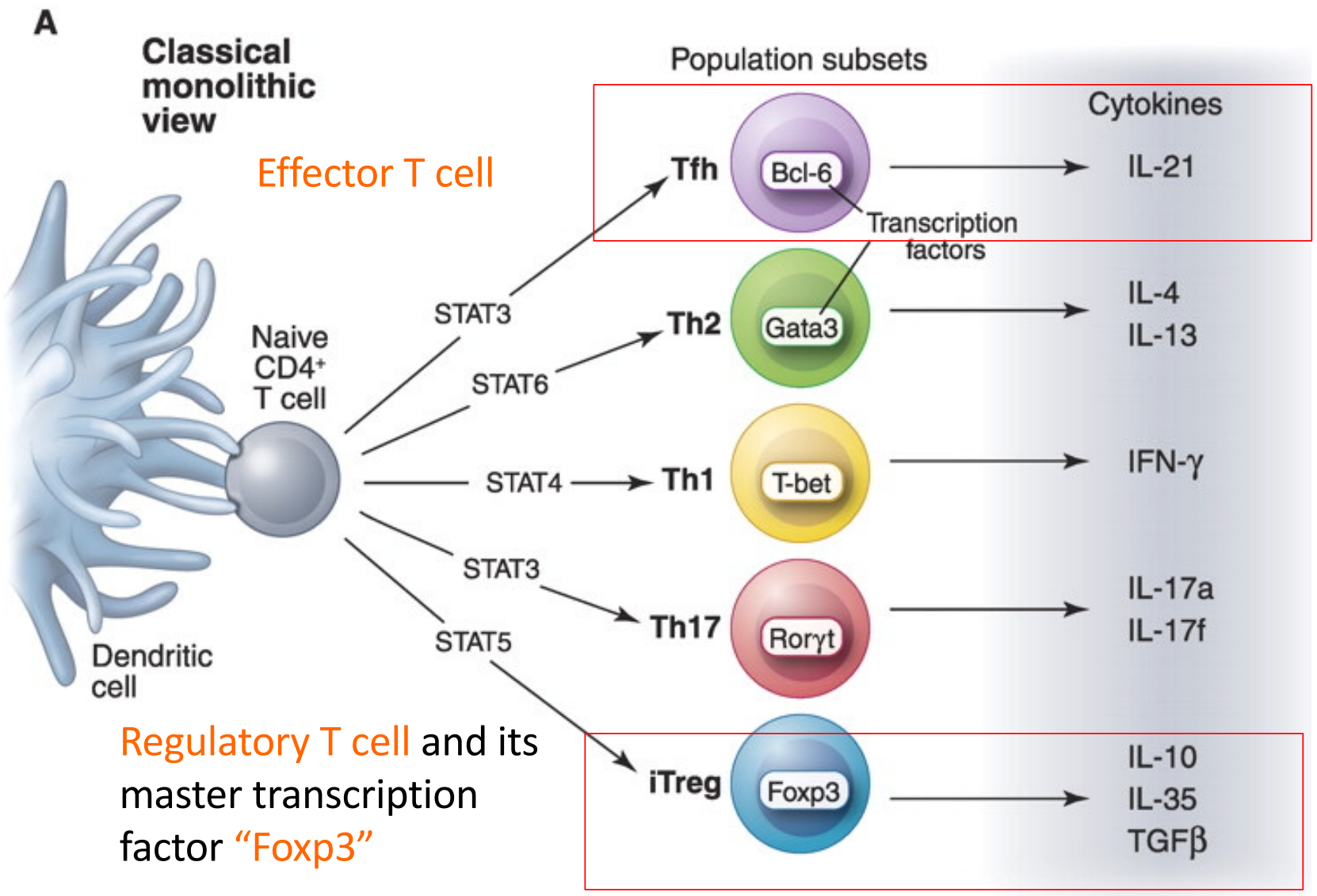
Cell *146*, 772–784 (2011)

Immunometabolims

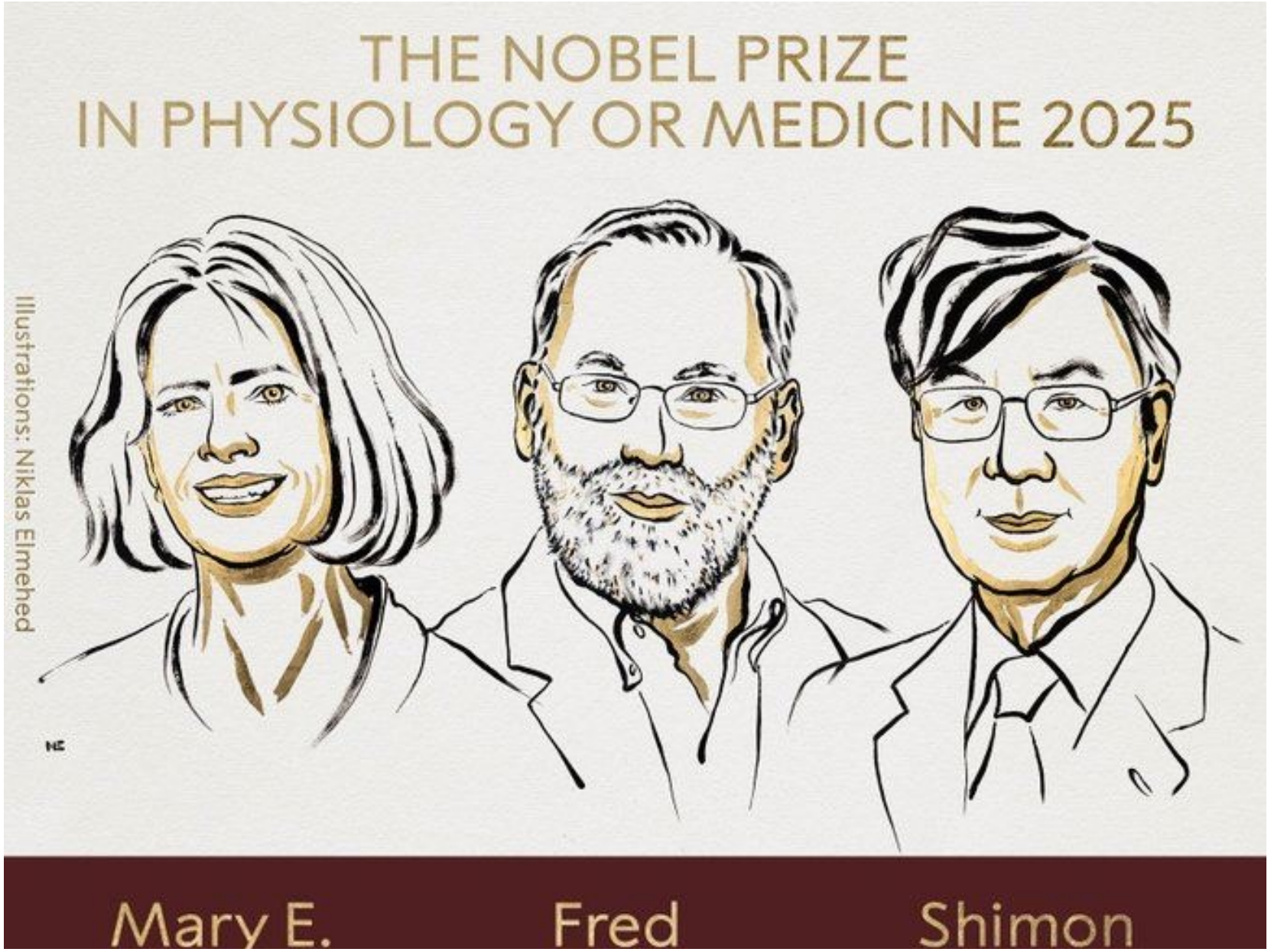
Micromanaging lupus nephritis

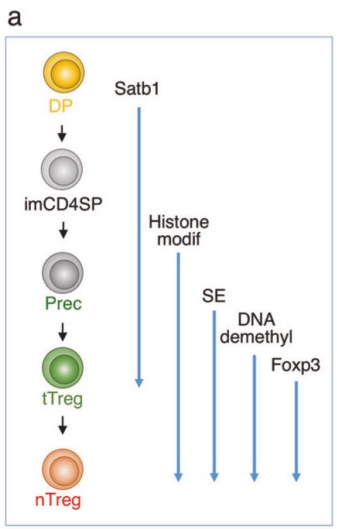
Glutamine and kidney disease

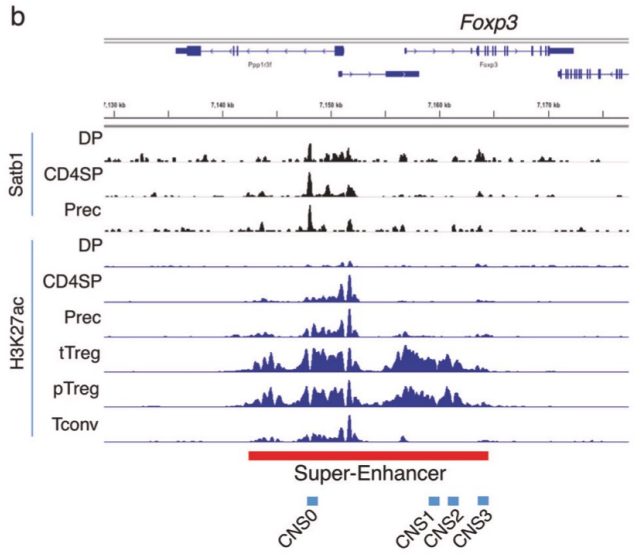




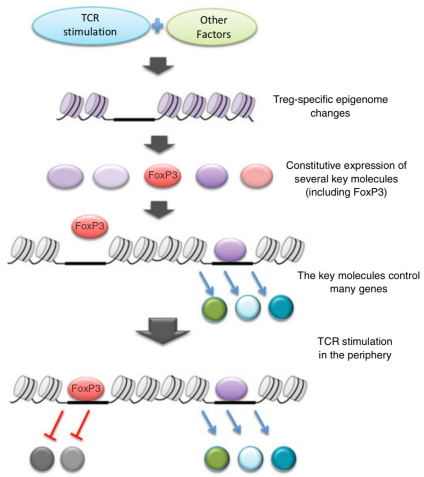
John J. O'Shea, and William E. Paul Science 2010;327:1098-1102

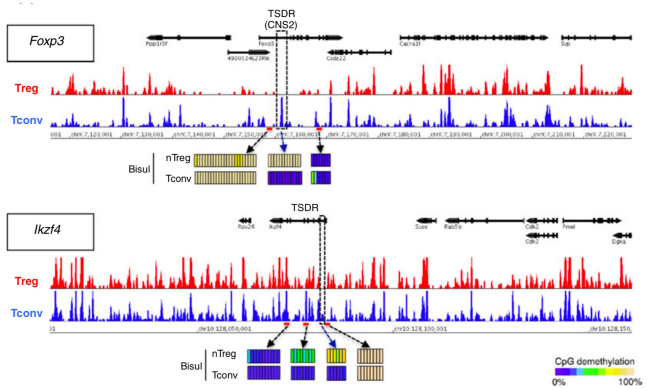

THE NOBEL PRIZE
IN PHYSIOLOGY OR MEDICINE 2025
Illustrations: Niklas Elmehed
Mary E.
Fred
Shimon



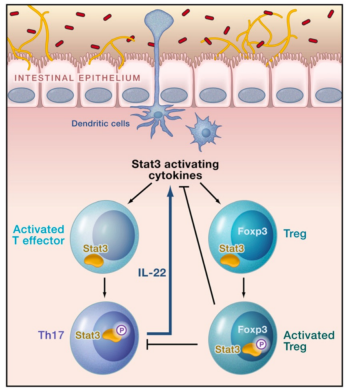


Foxp3 co-factors





Transcription factors in response to environment cues

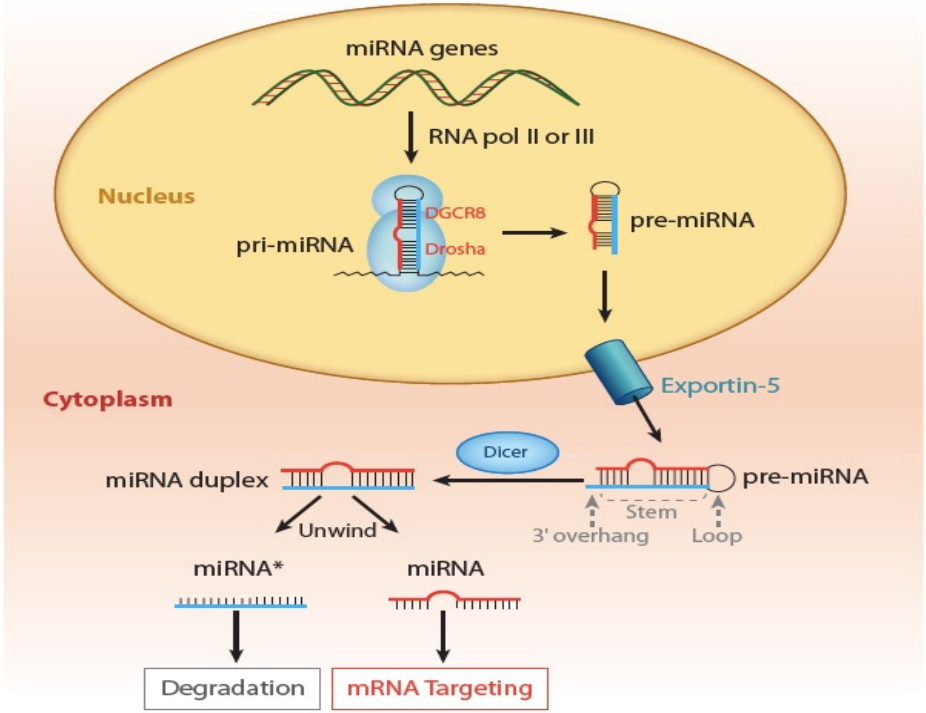


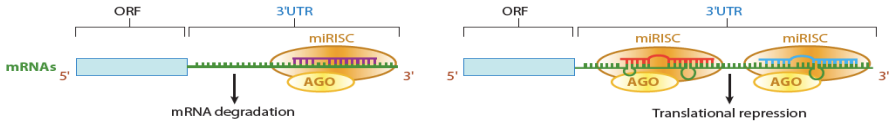
Immunological Reviews 2014; 259, 192-205
Immunity 2013; 38, 414-423
Cell 2010; 140, 845–858
Cell Research (2020) 30:465 – 474


Jedai
Skywalker
Activated Treg
Treg
IL-6
Darth Vader
Ex-Treg

microRNA ; miR

microRNA exists in humans and other eukaryotic organisms.
Regulates gene expression by silencing target mRNAs to control biology.

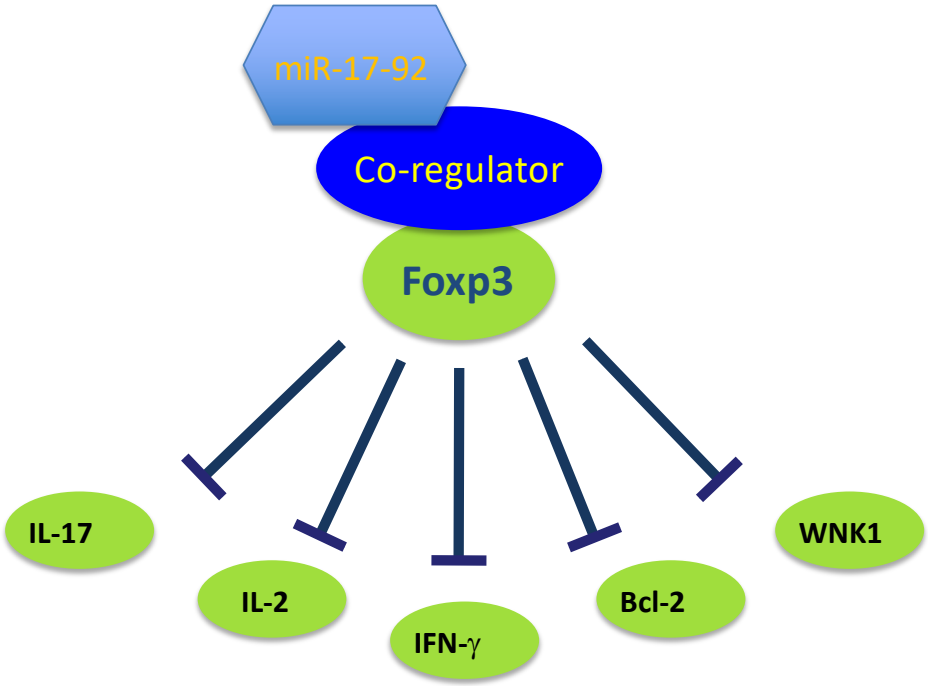




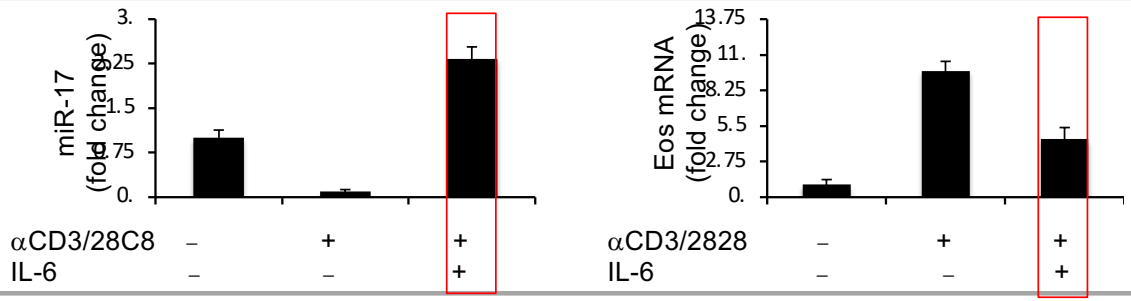
Annu. Rev. Biomed. Eng. 2010. 12:1–27

Hypothesis

- miR-17-92 target Foxp3 co-regulators
- Eos, a co-regulators, physically interacts with Foxp3 for inhibition multiple genes in Treg
- Knockdown of co-regulator derepress genes and decreases suppressive activity of Tregs in vitro and in vivo



HIF-1 binds to miR-17-92 promoter




```
Alignment block 1 of 4 in window, 115042880 - 115042970, 91 bps
B D           Mouse  ctagt--c---ata-cacgtgg-----ac------ct-agca-
B D             Rat  ctagt--c---ata-cacgtgg-----ac------cc-agca-
B D     Kangaroo rat  ccact--t---gtagcacgtgg-----ac------ct-cata-
B D   Naked mole-rat  ccagt--c---ata-cacgtggacctaac------ct-aacc-
B D       Guinea pig  ccagt--c---ata-cacgtgg-----ac------ct-aacc-
B D         Squirrel  ccagt--c---ata-cacgtgg-----ac------ct-aacc-
B D           Rabbit  ccagt--t---atc-cacgtgg-----ac------ct-aaca
B D             Pika  ccagt--t---acc-cacgtgg-----ac------ct-aaca
B D            Human  ccagt--c---ata-cacgtgg-----ac------ct-aact-
B D            Chimp  ccagt--c---ata-cacgtgg-----ac------ct-aact-
B D          Gorilla  ccagt--c---ata-cacgtgg-----ac------ct-aact-
B D        Orangutan  ccagt--c---ata-cacgtgg-----ac------ct-aact-
B D           Gibbon  ccagt--c---gta-cacgtgg-----ac------ct-aact-
B D           Rhesus  ccagt--c---ata-cacgtgg-----ag------ct-aact-
B D           Baboon  ccagt--c---ata-cacgtgg-----ag------ct-aact-
B D         Marmoset  ccagt--cattata-cacgtgg-----ac------ct-aact-
B D  Squirrel monkey  ccagt--catcata-cacgtgg-----ac------ct-aact-
B D          Tarsier  ccagt--c---ata-cacgtgg-----ac------ct-aact-
B D      Mouse lemur  ccagt--c---ata-cacgtgg-----ac------ct-aact-
B D        Bushbaby  ccagt--c---ata-cacgtgg-----ac------ct-aact-
B D      Tree shrew  agact--c---ata-cacgtgg-----ac------ct-aact-
B D             Pig  ctagt--c---ata-cacgtgg-----ac------ct-aact-
B D         Dolphin  ccagc--c---ata-cacgtgg-----ac------ct-aact-
B D           Sheep  ccagt--c---ata-cacgtgg-----ac------ct-aact-
B D             Cow  ccagt--c---ata-cacgtgg-----ac------ct-aact-
B D             Cat  ccagt--c---ata-cacgtgg-----ac------ct-aact-
B D             Dog  ccagt--c---ata-cacgtgg-----ac------ctaaact-
B D           Panda  ccagt--c---ata-cacgtgg-----ac------ct-aact-
B D           Horse  ctagt--c---ata-cacgtgg-----ac------ct-aact-
B D         Microbat  tcatt--c---ata-cacgtgg-----ac------ct-aact-
B D         Megabat  ccagt--c---ata-cacgtgg-----ac------ct-aact-
B D        Hedgehog  gcagtccc---aca-cacgtgg-----accggacact-aact-
B D        Elephant  acagt--g---ata-cacgtgg-----ac------at-aact-
B D      Rock hyrax  agagc--g---ata-cacgtgg-----ac------ct-aact-
B D          Tenrec  ccagc--g---ata-cacgtgg-----ac------ct-aact-
B D         Manatee  acagt--g---ata-cacgtgg-----gc------ct-aact-
B D       Armadillo  ccagt--c---ata-cacgtgg-----ac------ct-aact-
B D     Zebra finch  acagt--t---tca-ctcattt-----aa------ag-gaga-
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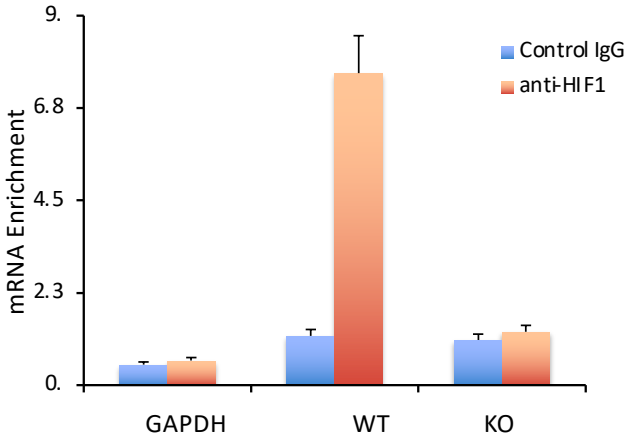


Mir17-92 target foxp3 co-regulators

Target scan prediction

Eos

```
    3' gauggacgugacauucGUGAAAc 5' mmu-miR-17
                       ||||||
489:5' uauuuaucugacccuuCACUUUu 3' Ikzf4
```

IRF4

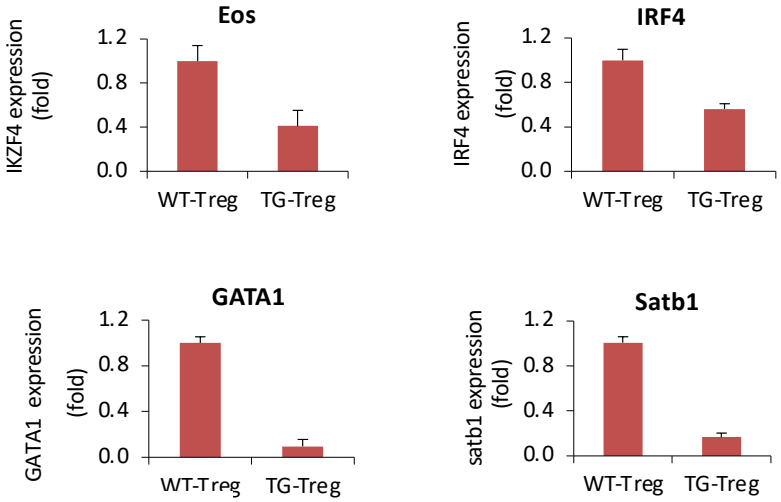
```
    3' gauggacgugacauucGUGAAAc 5' mmu-miR-17
                       ||||||
1966:5' cccccaguucauguuuCACUUUa 3' Irf4
```

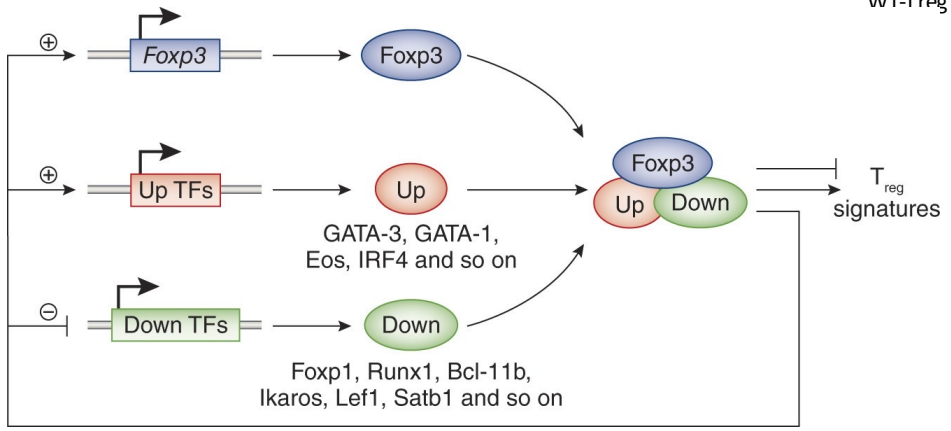
Satb1

```
    3' agUCAAAACGUAUCUAAACGUGu 5' mmu-miR-19a
         | | || |: | | ||||||
105:5' ugAAUCUU-CGGAAACUUGCACa 3' Satb1
```

```
    3' agucaaaacguaccuaAACGUGu 5' mmu-miR-19b
                       ||||||
104:5' augaaucuucggaaacUUGCACa 3' Satb1
```

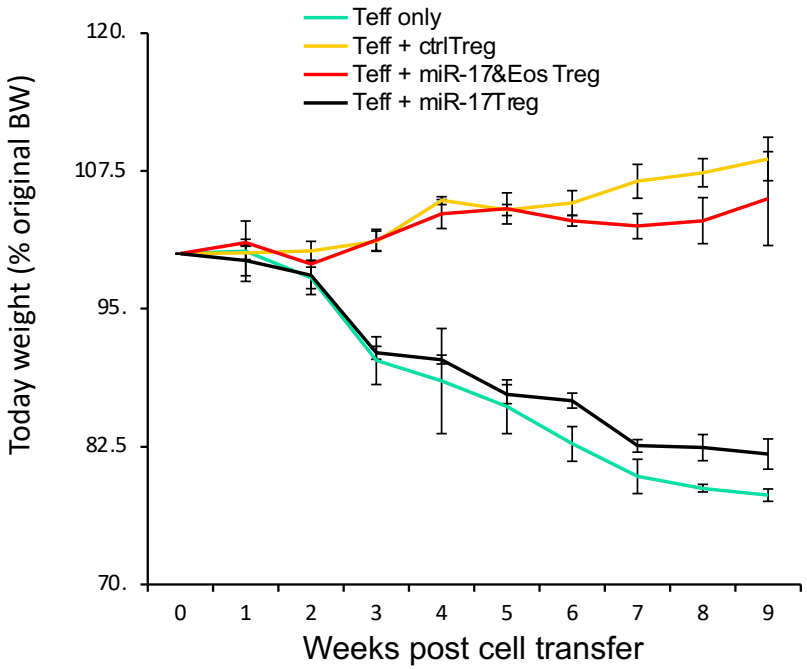
miR-17-92 overexpression mice

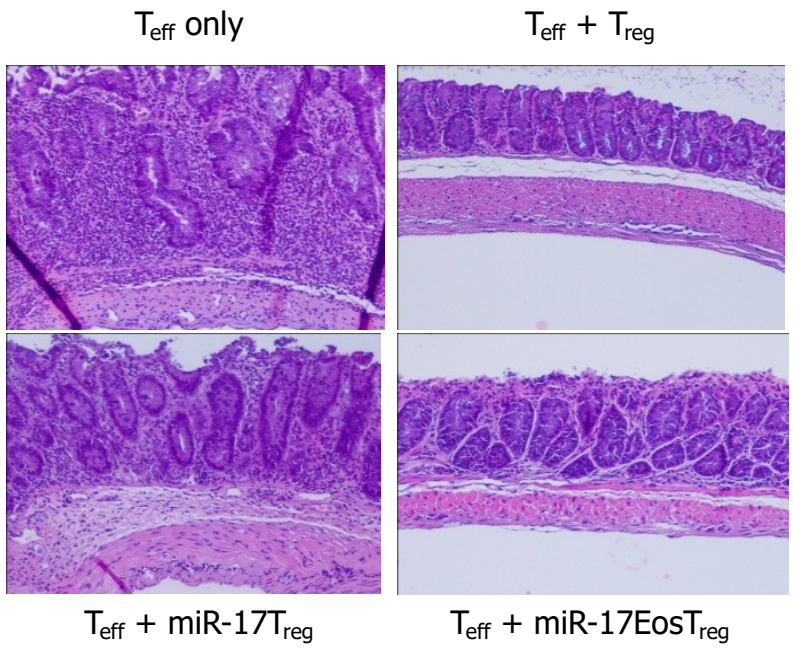




Nature Immunology volume 13, 943–945(2012)

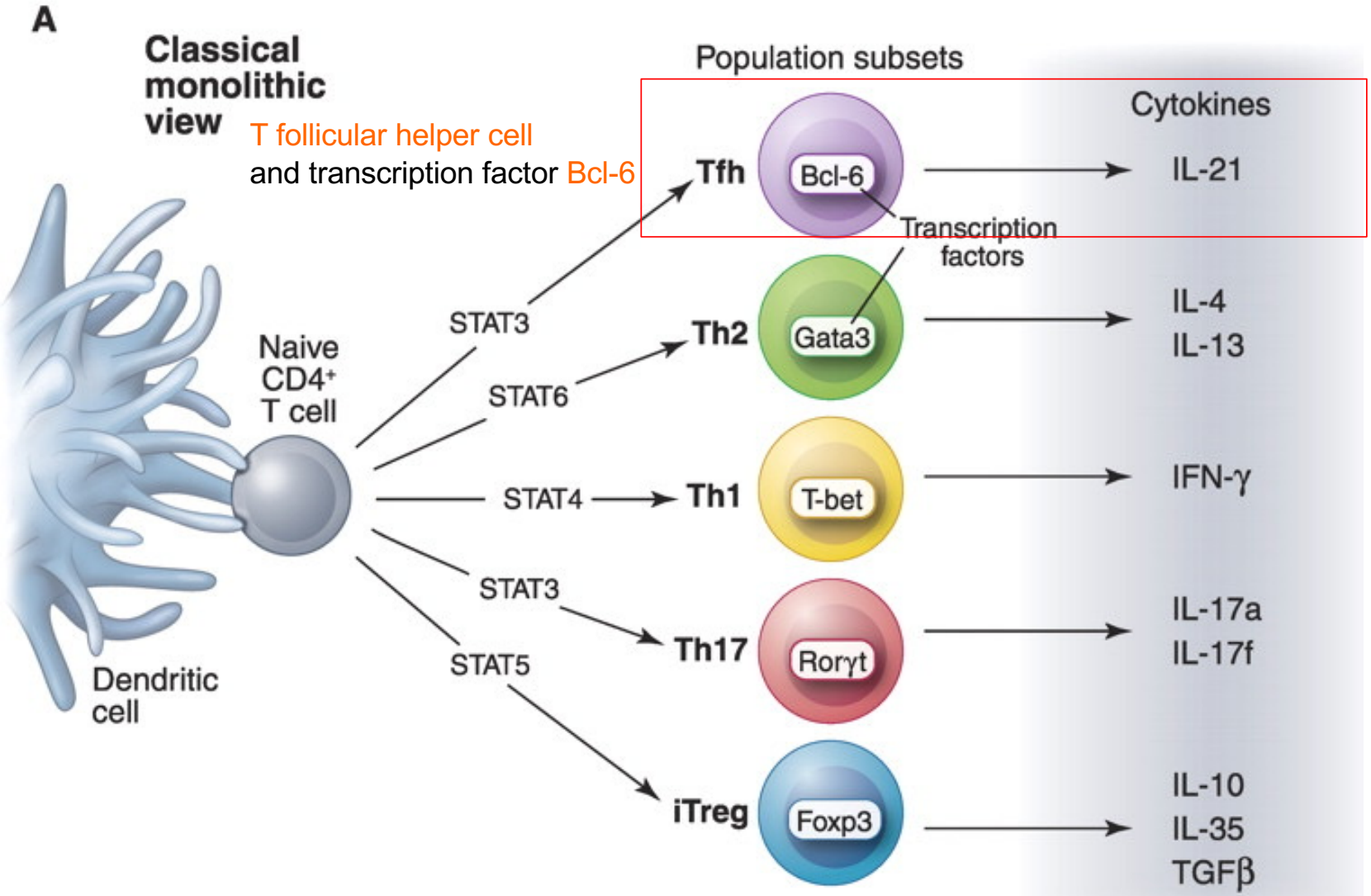
- Colitis model (iv transfer Teff $5x10^5$,Treg $1x10^5$ into Rag2 KO mice)



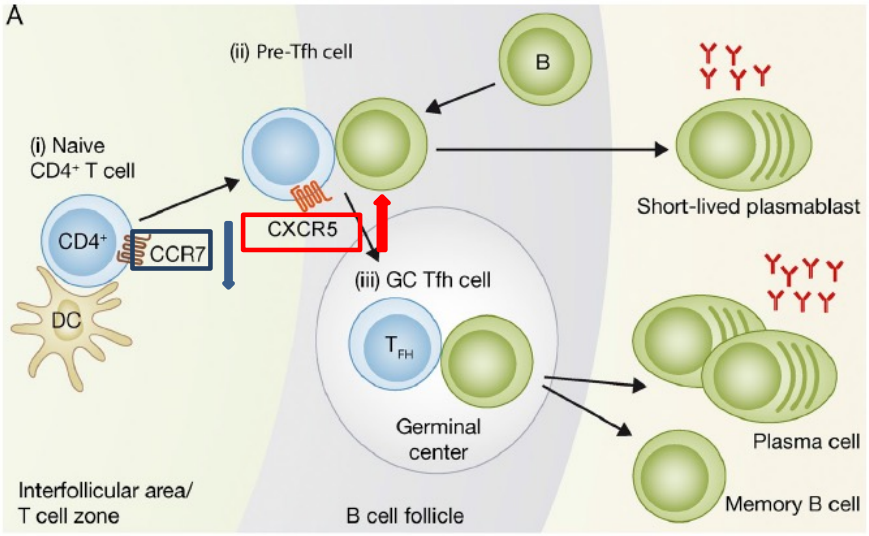


Immunity 45, 83–93 (2016)

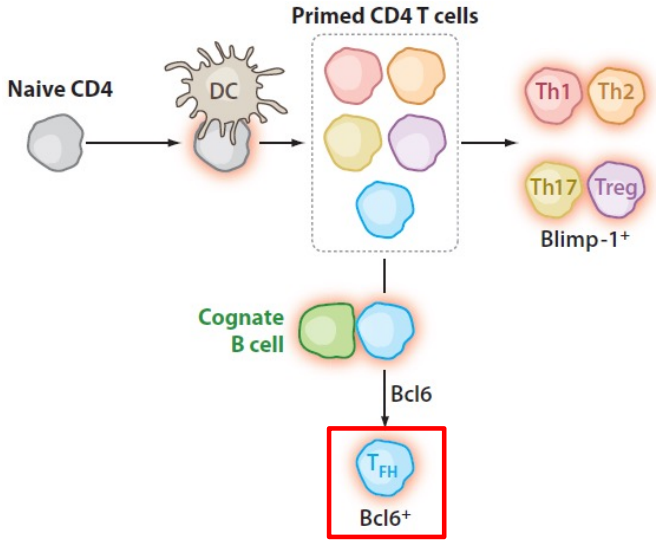

Jedai
Skywalker
Foxp3 co-factors
Activated Treg
Treg
miR-17-92
Darth Vader
Ex-Treg



John J. O'Shea, and William E. Paul Science 2010;327:1098-1102



J. Exp. Med. 2012 Vol. 209 No. 7 1241-1253



Annu. Rev. Immunol. 2011. 29:621–63

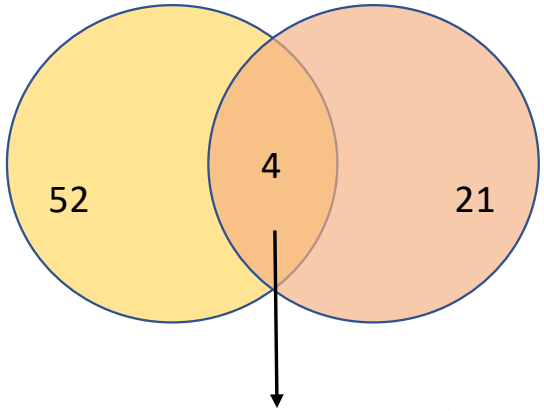
The development of T_{FH} cells is initiated by and dependent on their movement out of the T-cell zone and into the B-cell follicle. This migration process is regulated by upregulation of CXCR5 as well as downregulation of both CCR7 and P-selectin glycoprotein ligand 1 (PSGL1).

T_{FH} cells have unique developmental regulation and Bcl6 was reported to be selectively expressed in T_{FH} cells. However, although Bcl6 potentiates T_{FH}-cell generation in vivo, recent data suggest that it may not regulate CXCR5 upregulation by activated T cells or their migration to B-cell follicles in vivo.

The transcriptional mechanisms underlying initial T_{FH}-cell commitment remain unclear.

Up-regulated miRNA in
SLE plasma
(3 SLE / 3 healthy donor)

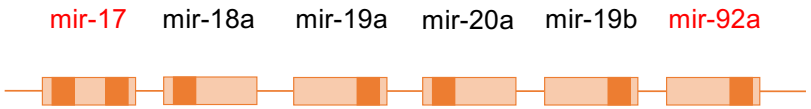
Up-regulated miRNA in
SLE CD3+ T cells
(GSE13887, 10 SLE /9 healthy donor)



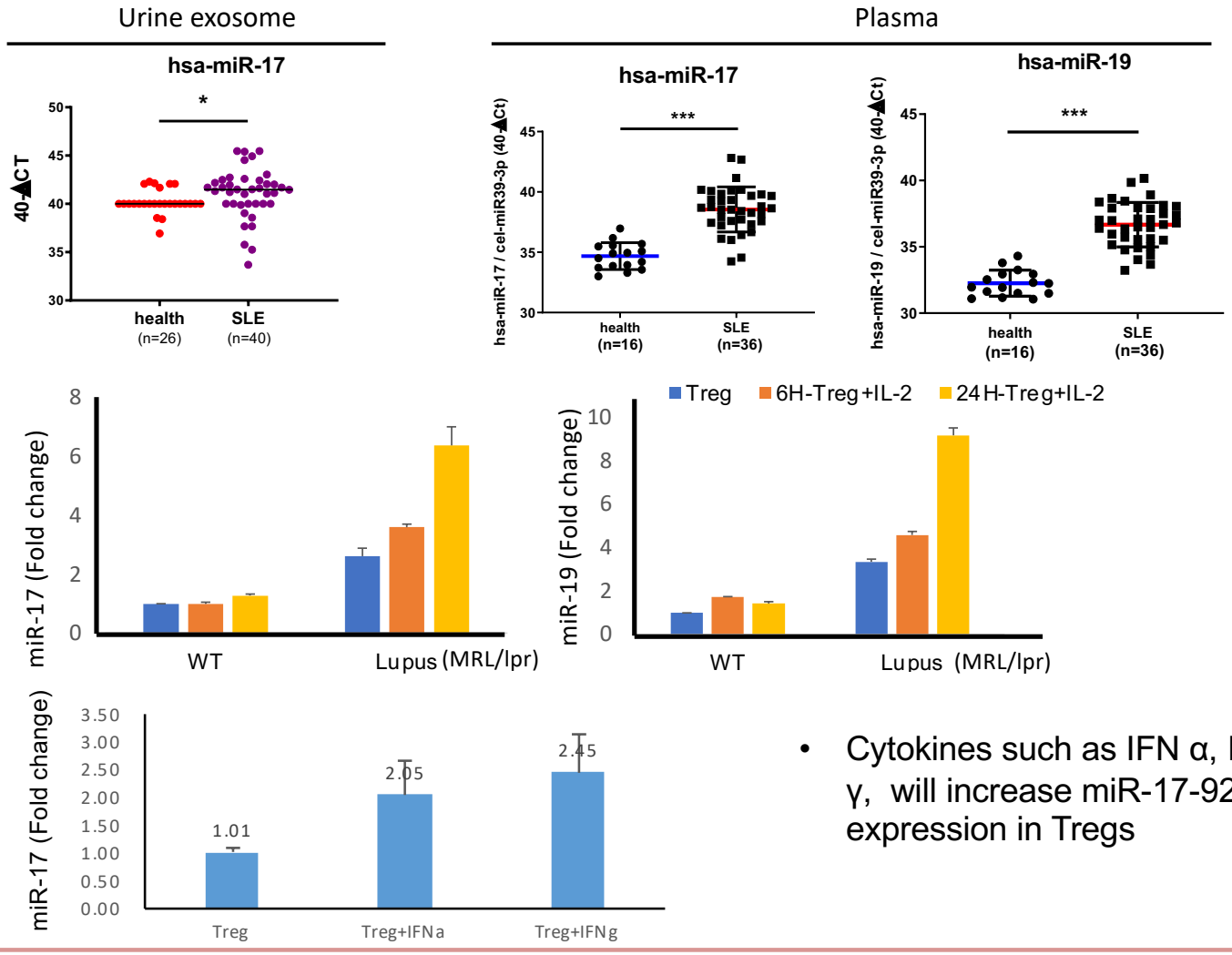
Eos target prediction

Let7-b	X
Let7-d	X
Mir-17-92	0
Mir-6125	X

miR17-92 cluster



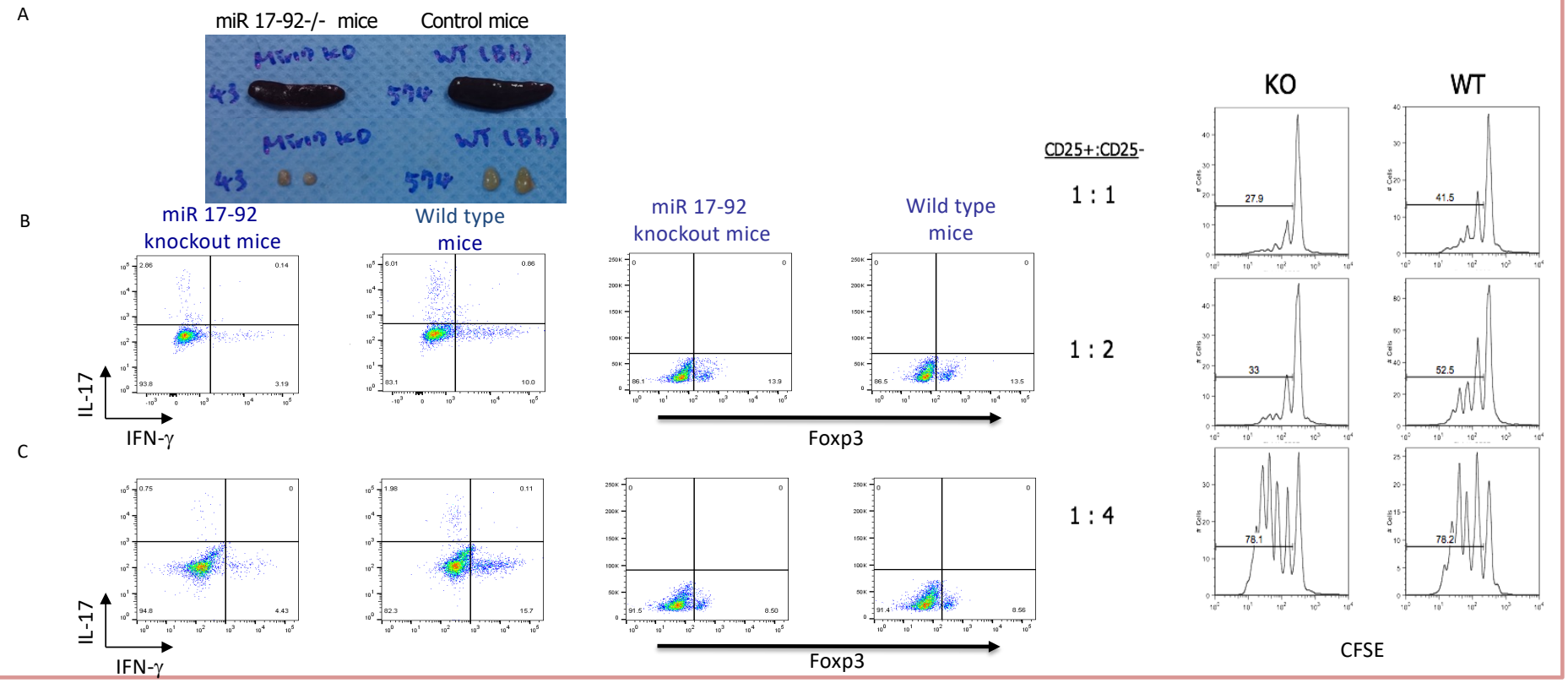
miR-17-92 up-regulated in lupus nephritis



- Cytokines such as IFN α, IFN γ, will increase miR-17-92 expression in Tregs

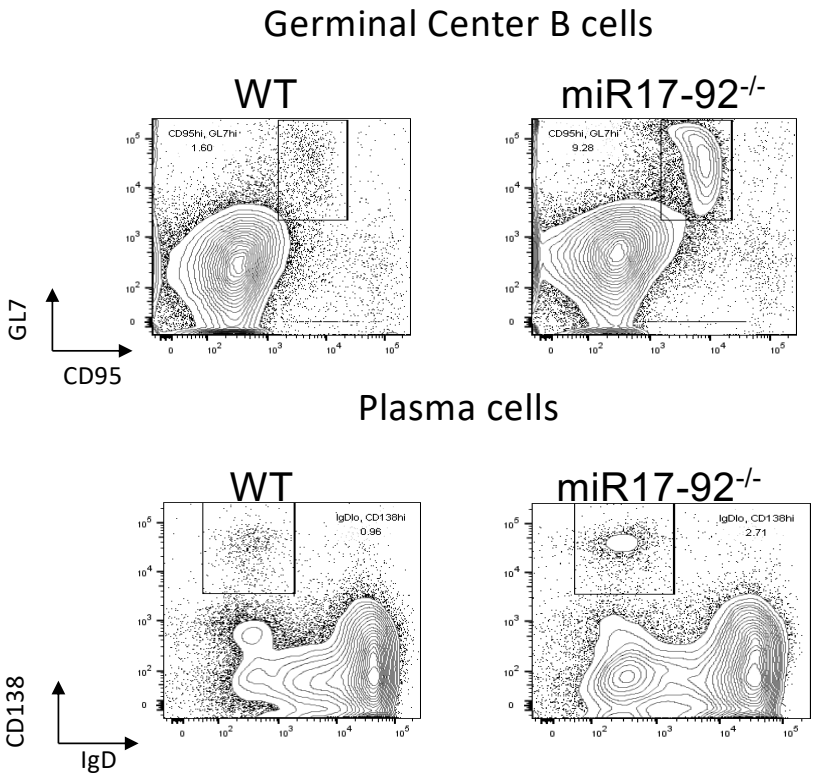
miR17-92 CD4 T cell specific knockout alleviate lupus nephritis

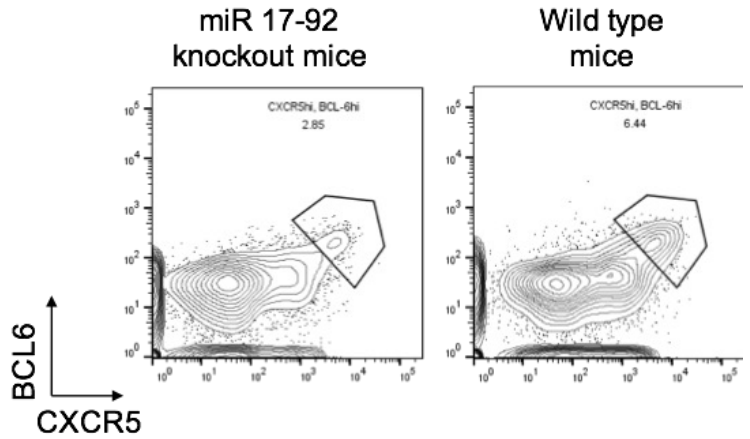
- miR17-92 CD4 T cell specific knockout improved pristane induced lupus nephritis
  - Alleviate splenomegaly and lymphadenopathy
  - Decrease Th17 and Th1

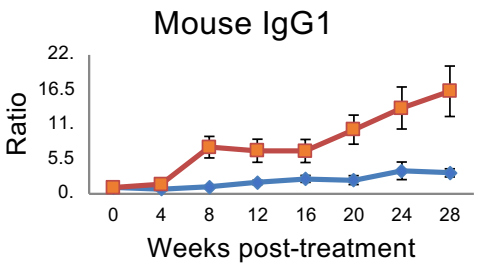


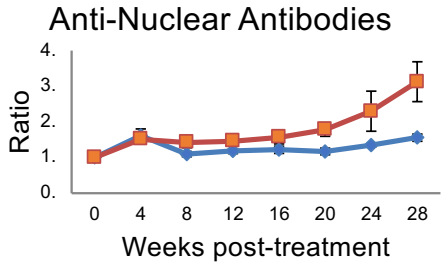
miR17-92 CD4 T cell specific knockout reduce GC response

- miR17-92 CD4 T cell specific knockout decrease autoimmune response
  - Decrease TFH
  - Decrease germinal center B cells, plasma cells and autoantibody



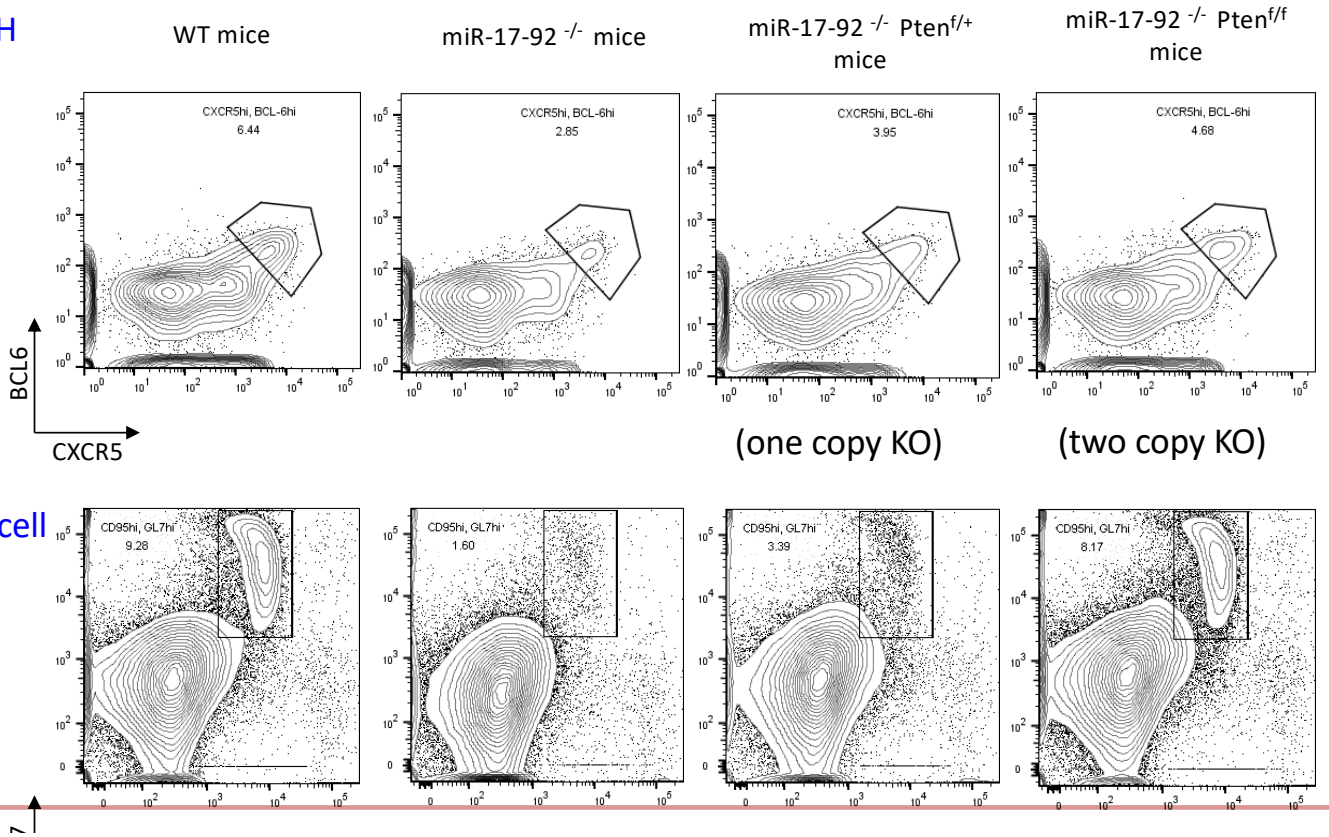




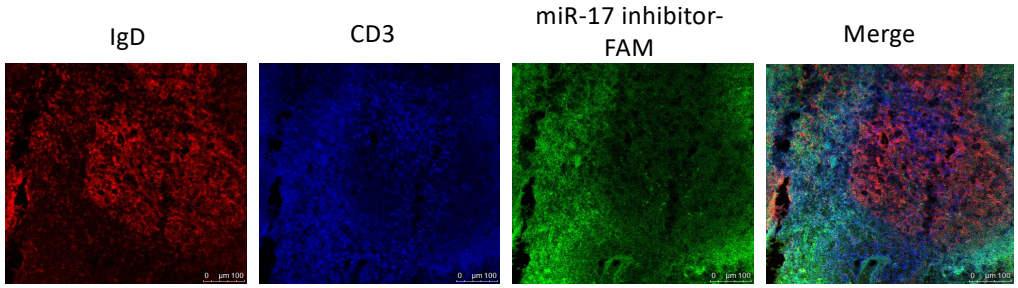


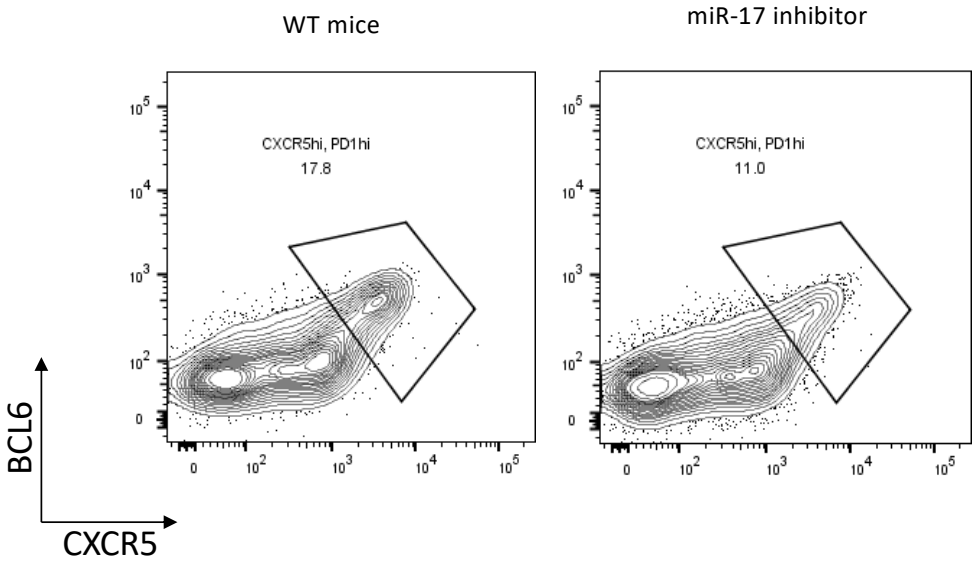
miR17-92 knockout diminished Thf by targeting PTEN-PI3K axis

- miR17-92 CD4 T cell specific knockout X Pten T cell specific knockout
  - Rescue Tfh partially



miR-17 antagonist impaired autoimmune response by diminishing TFH

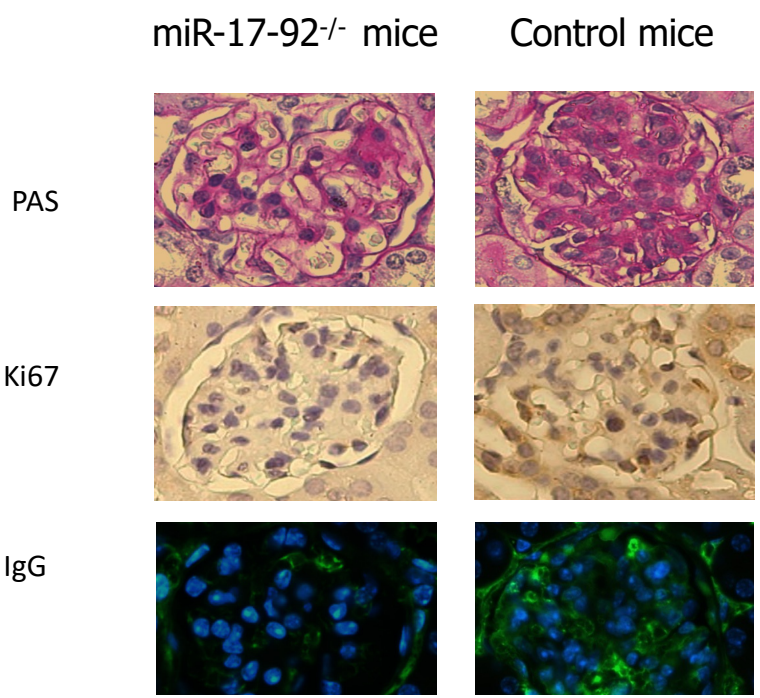




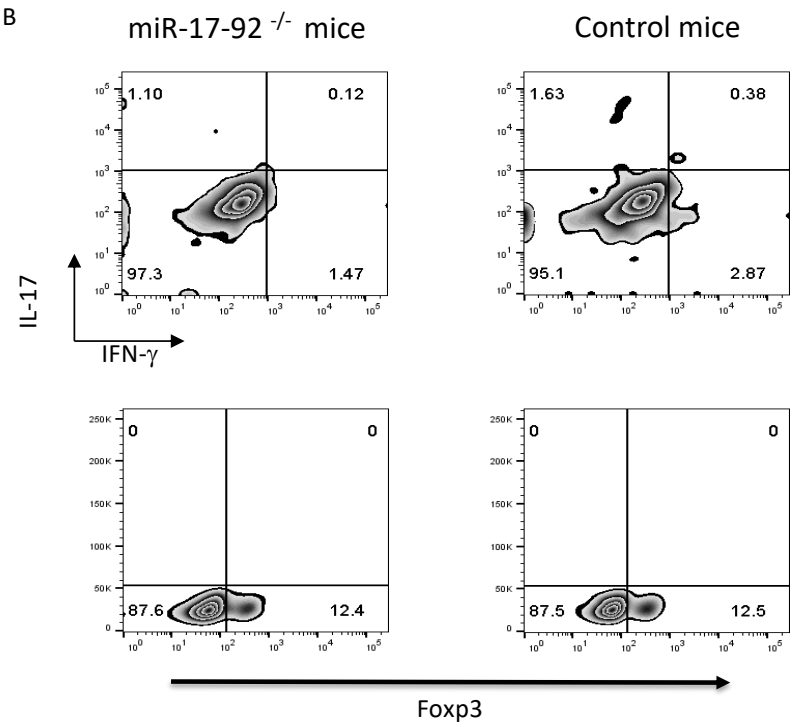
miR17-92 CD4 T cell specific knockout alleviate lupus nephritis

- miR17-92 CD4 T cell specific knockout
  - Alleviate lupus nephritis
  - Decrease Th17 and Th1 infiltration in kidney

A



B

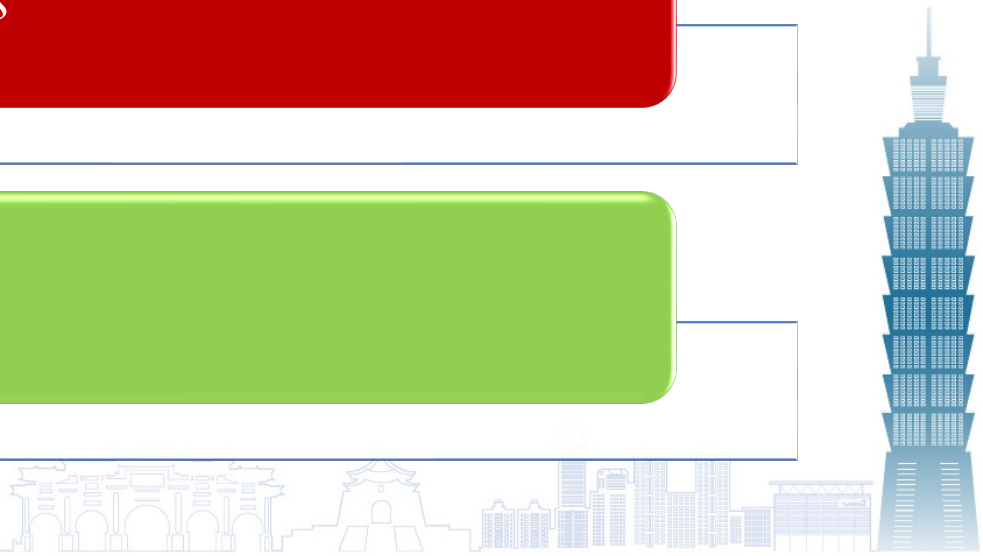



Jedai
Foxp3 co-factors
Activated Treg
Skywalker
Treg
miR-17-92
Darth Vader
TFH
Ex-Treg

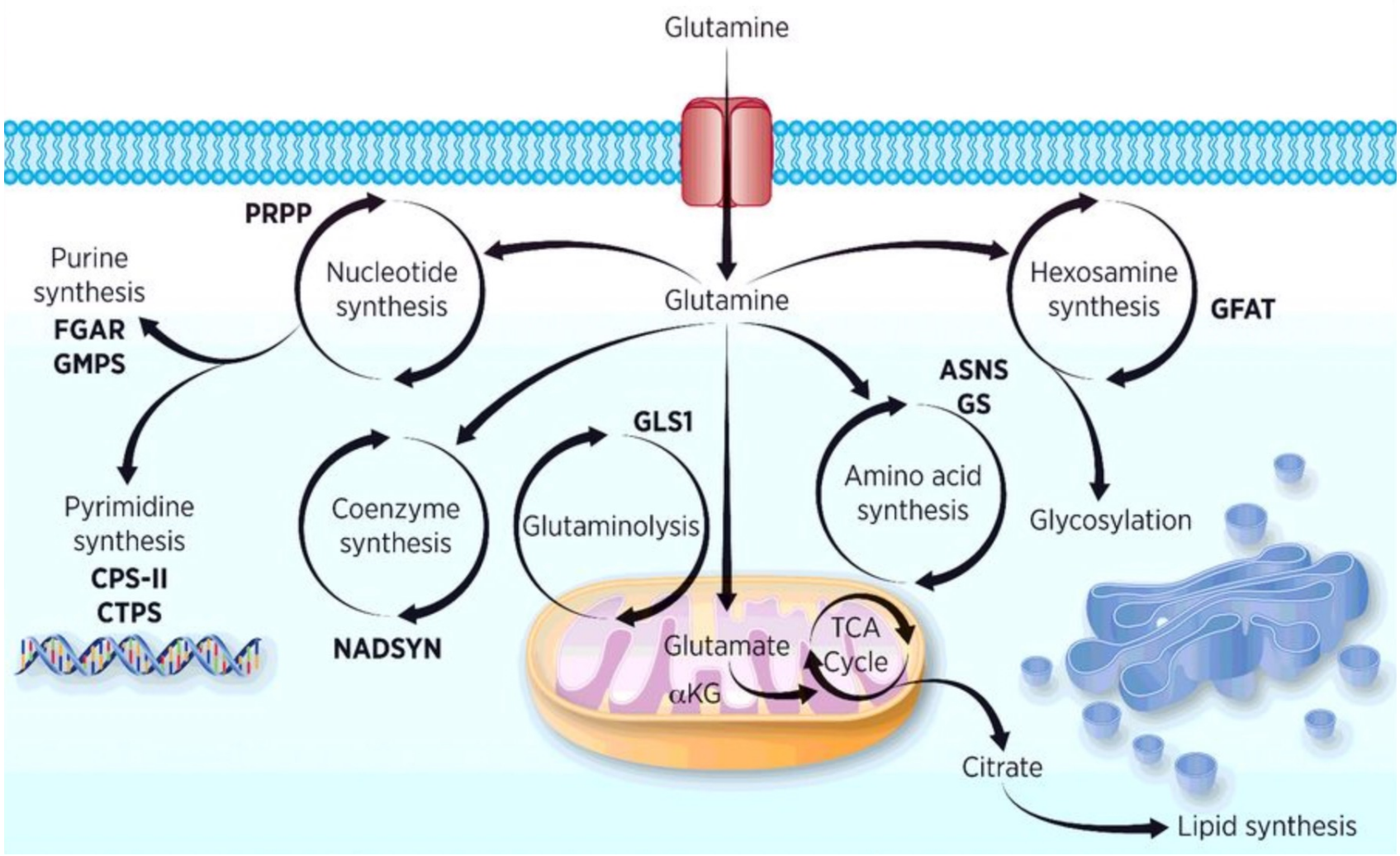
Immunometabolims

Micromanaging lupus nephritis

Glutamine and kidney disease



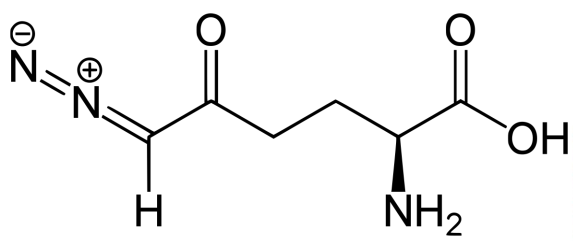
Glutamine, the most abundant amino acid in our body



Mol Cancer Ther; 17(9); Sep 2018

6-Diazo-5-oxo-L-norleucine (DON)

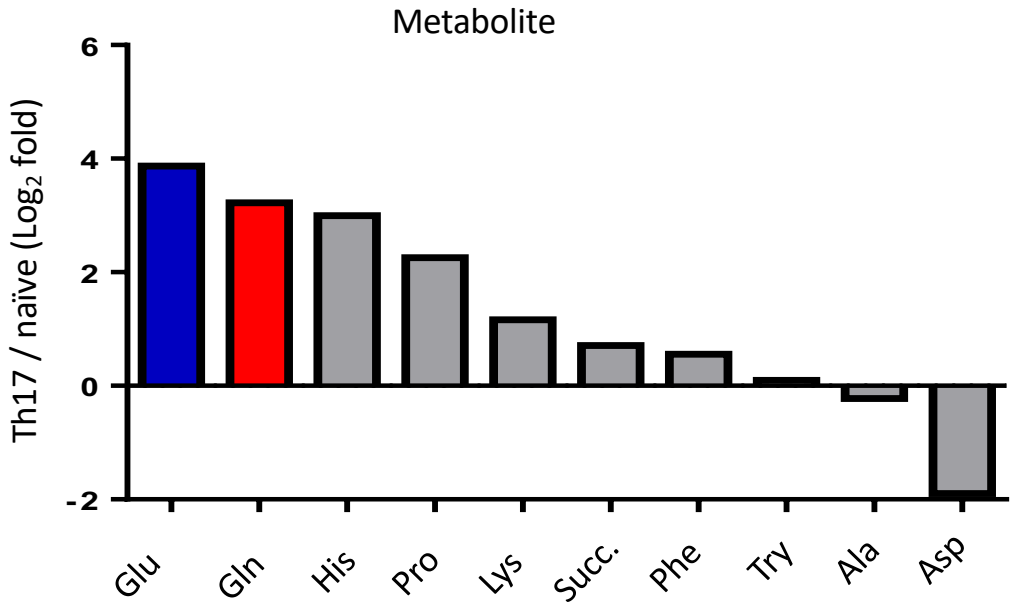
- an unconventional amino acid having a structure similar to glutamine
- DON broadly blocks glutamine utilizing pathways in cancer cells



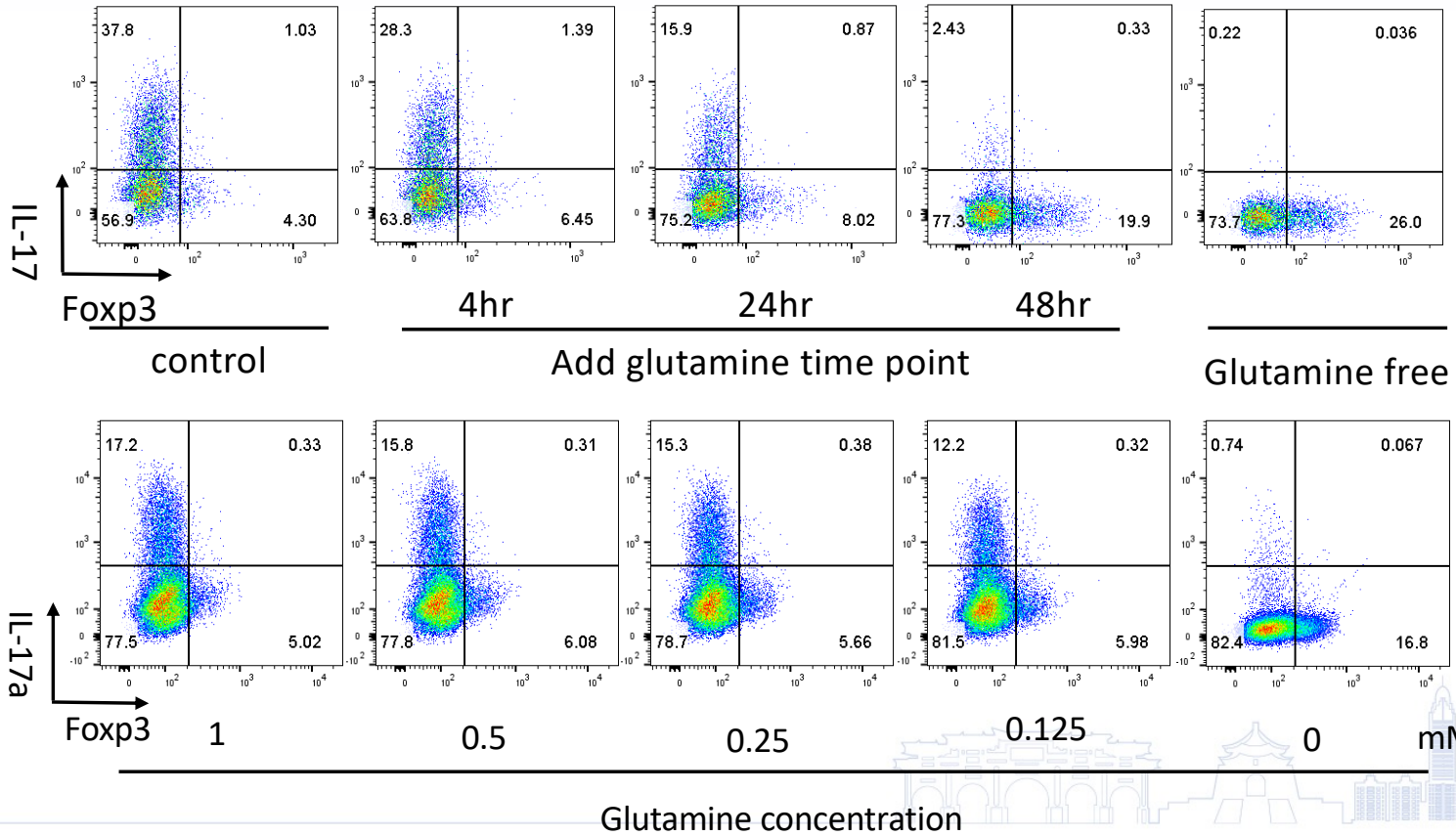
DON

Role of glutamine metabolism in kidney injury?

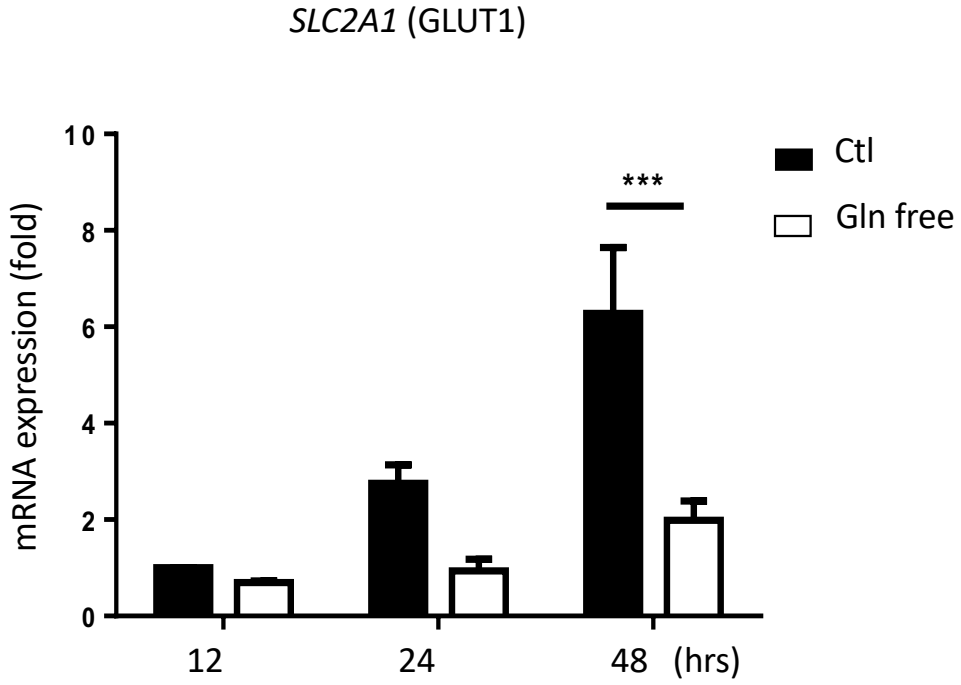
Th17/naive T cells intracellular amino acid abundance over time



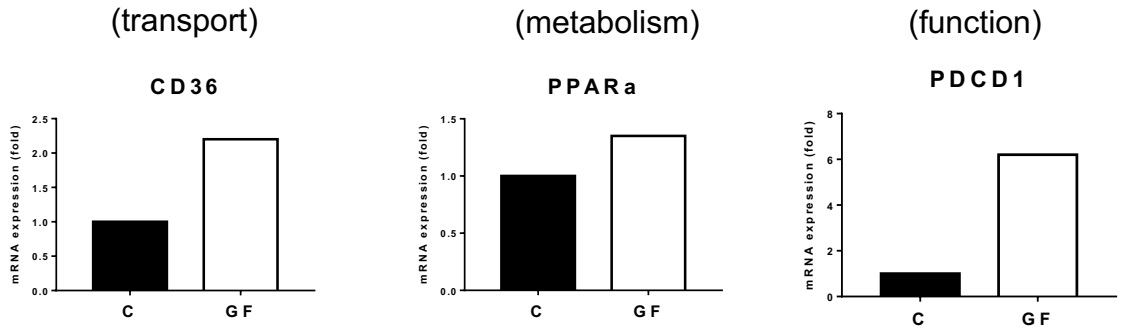
TH17 polarization condition with glutamine-free medium (GF) that replete glutamine at different time point/ with different concentration

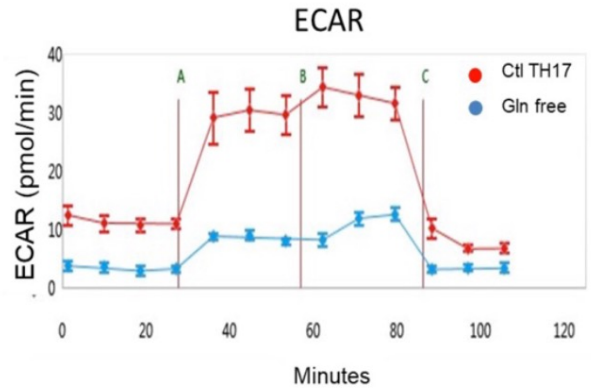


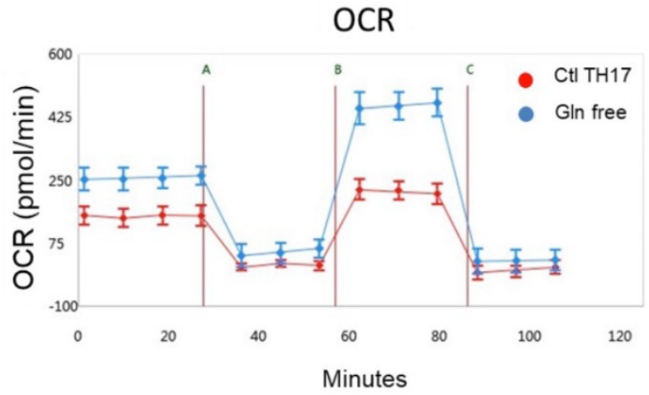
Decreased SLC2A1 (Glucose transporter 1 or GLUT1) mRNA in GF condition



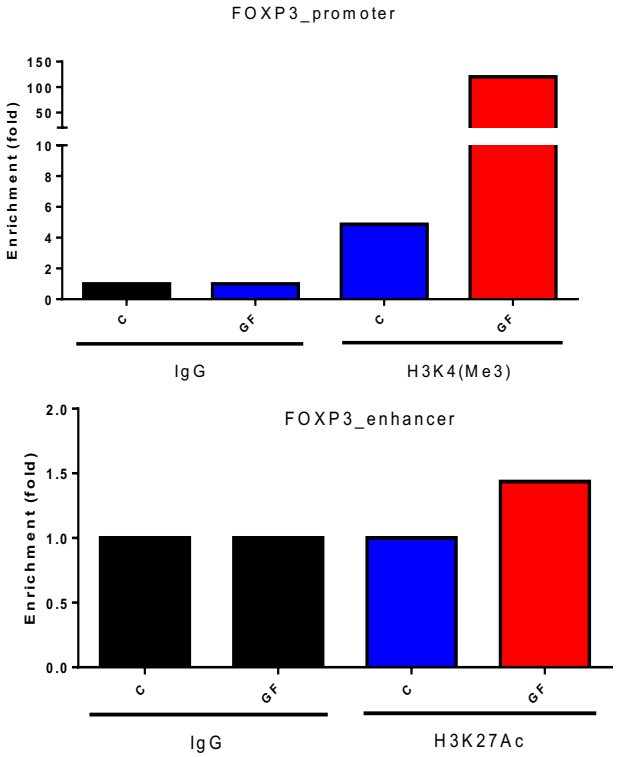
Fatty acid metabolism modulate polarization of Gln-free induced Treg

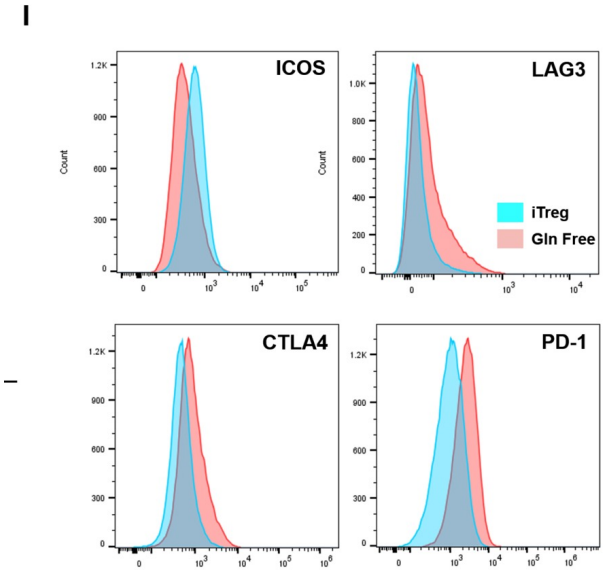


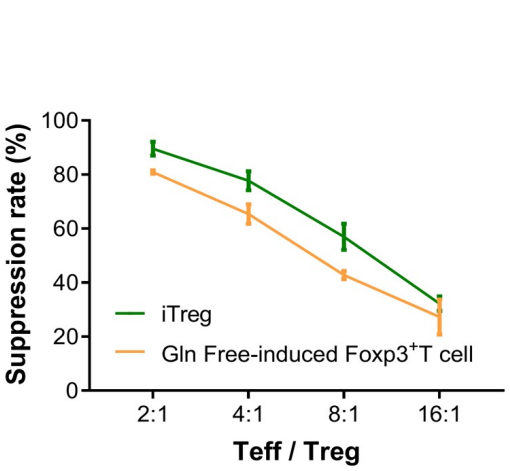




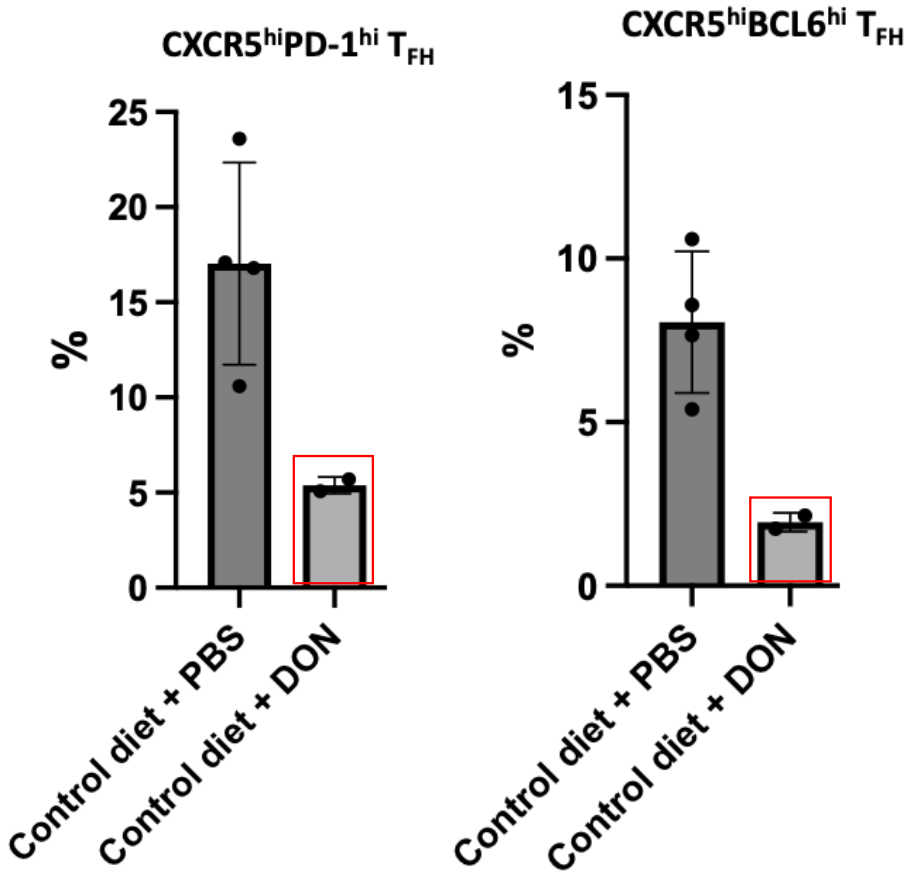
Glutamine modulate epigenetic regulation on the promoter/enhancer of Foxp3

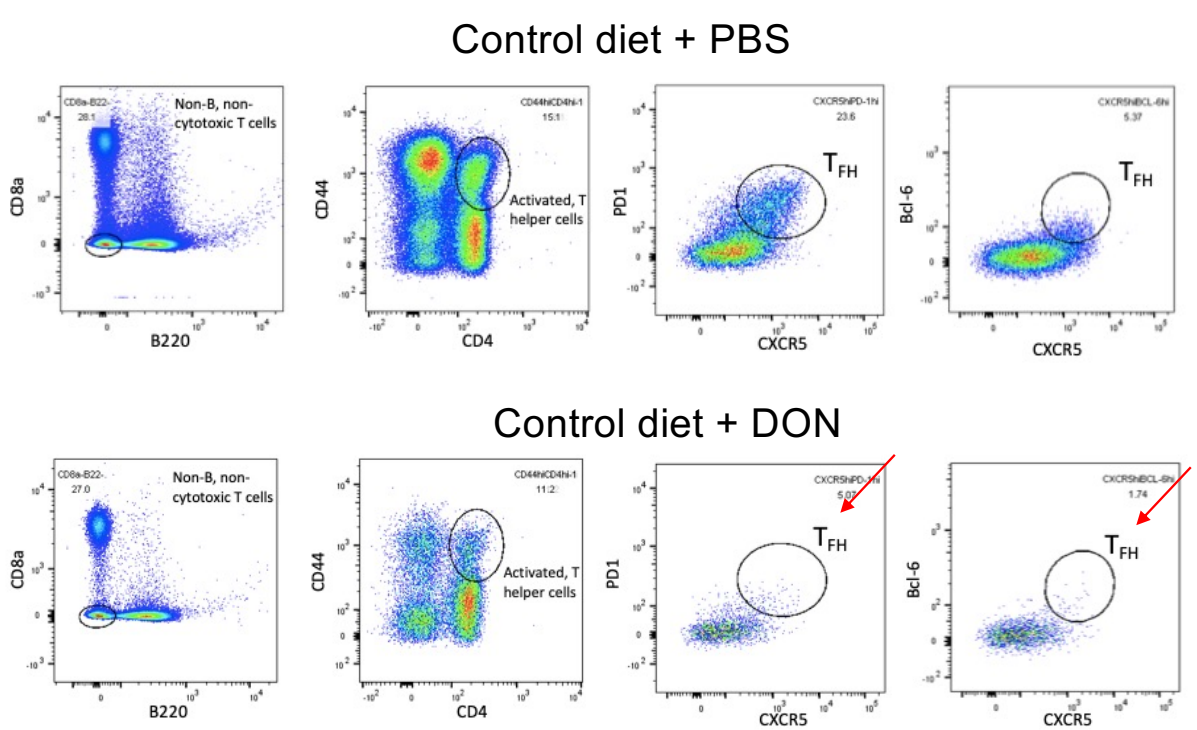




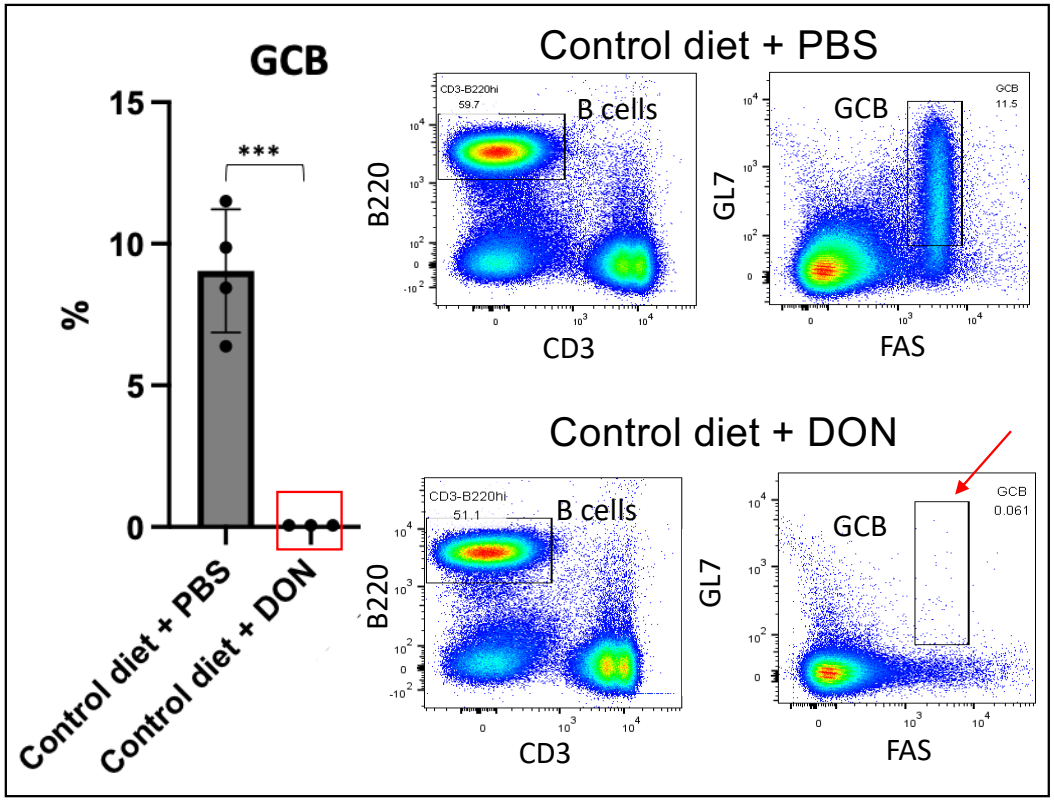


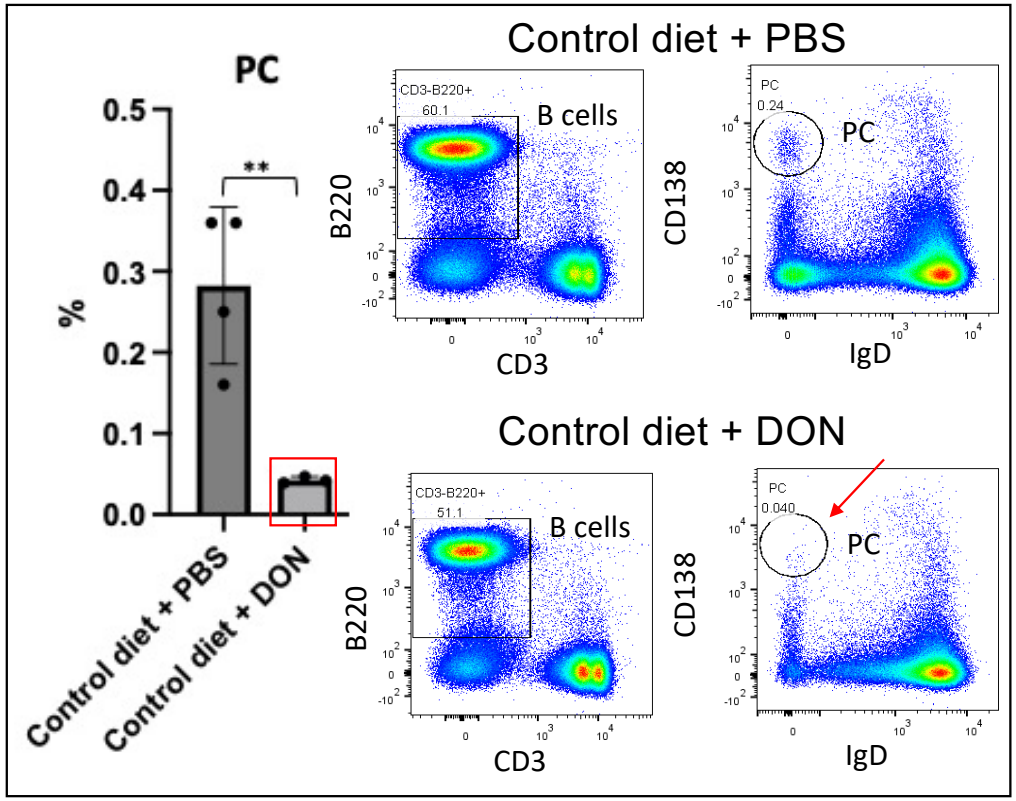
DON inhibits follicular helper T cells differentiation



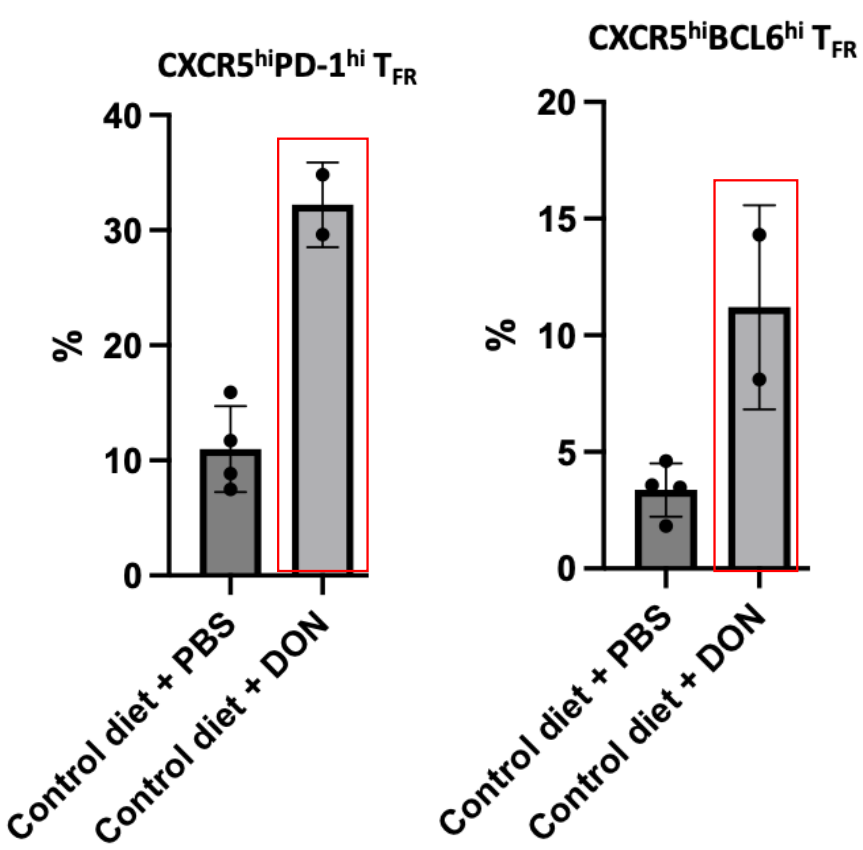


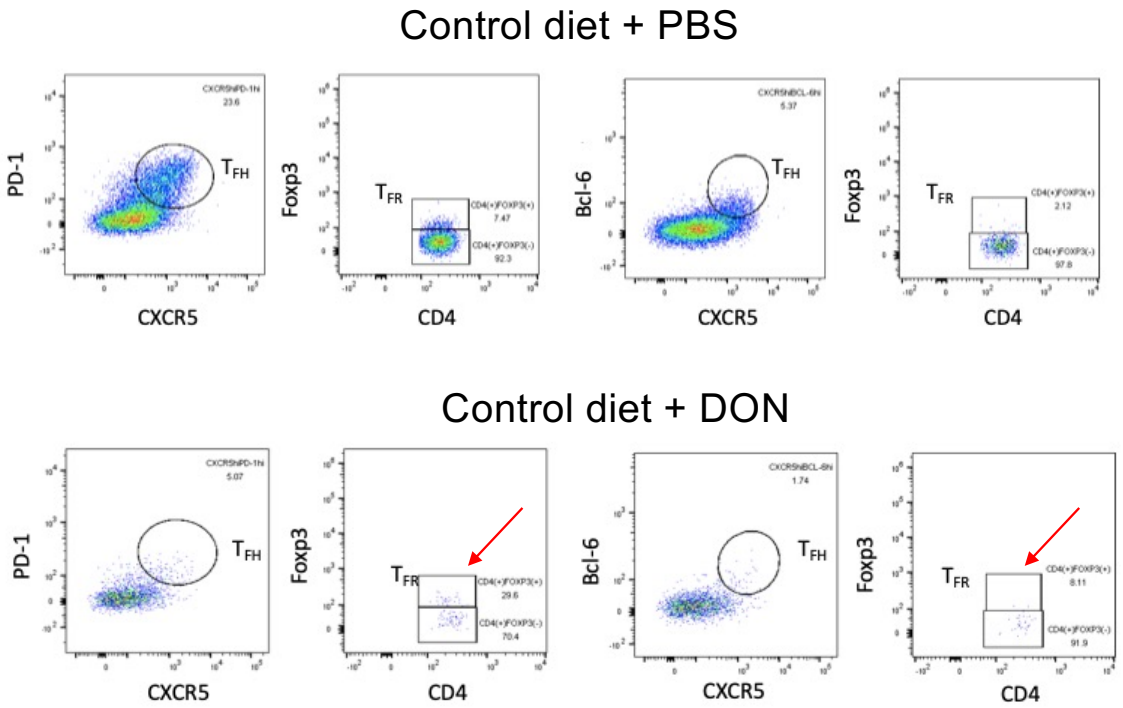
DON inhibits germinal center B cells and plasma cells differentiation



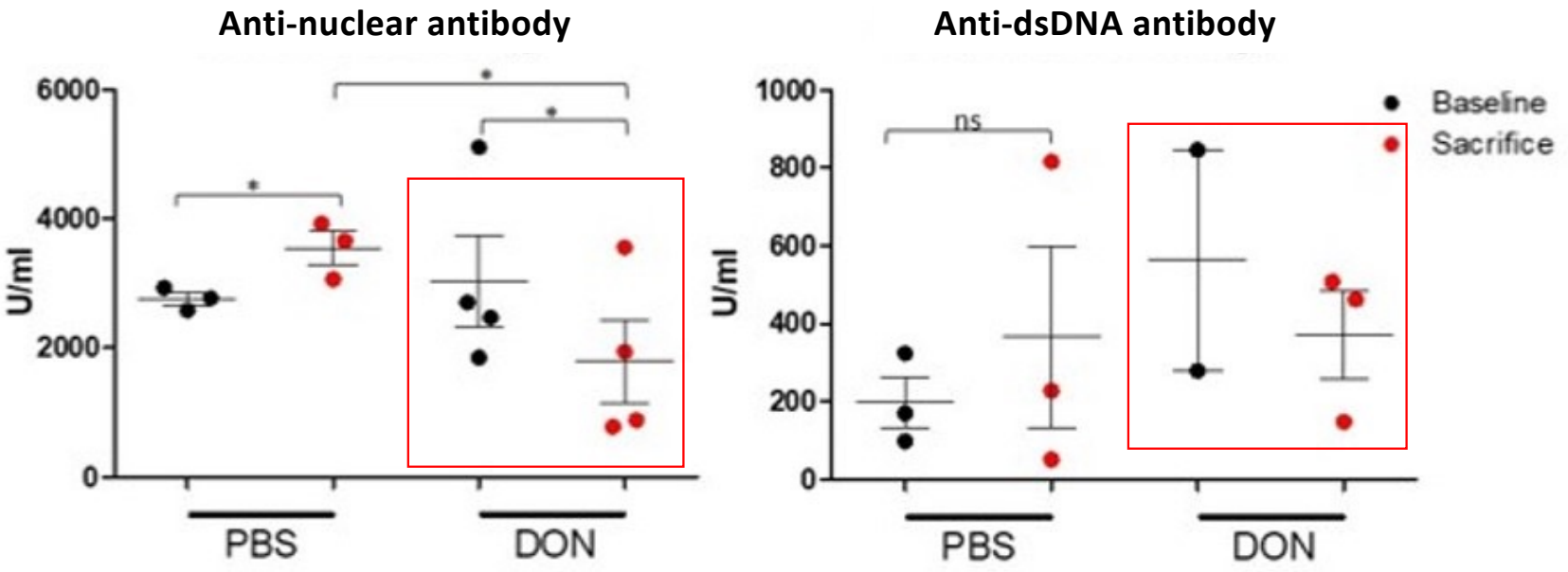


DON enhances follicular regulatory T cells differentiation

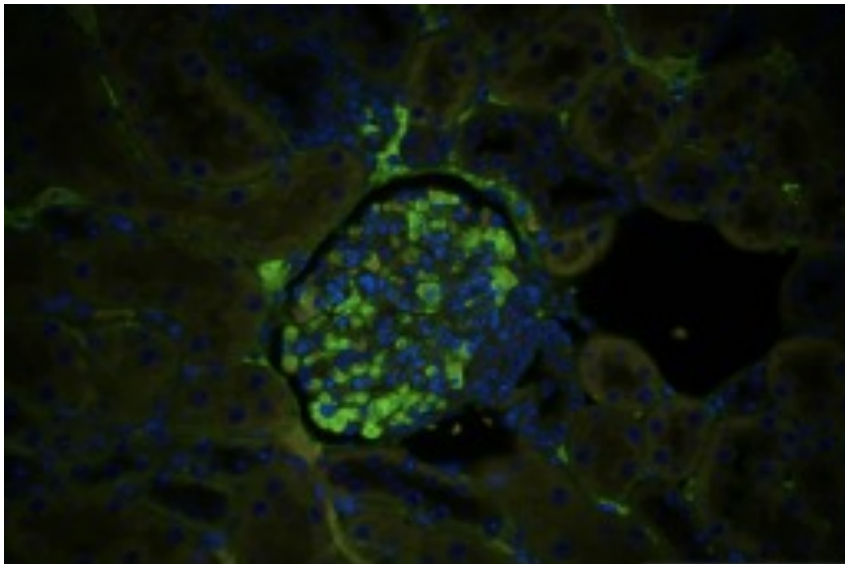


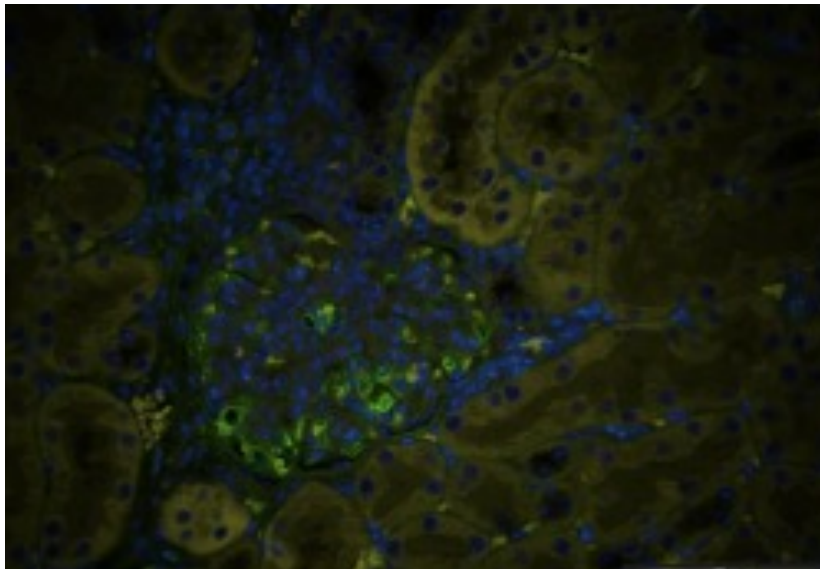


- DON prevents elevation in serum autoantibody levels in mice with early SLE

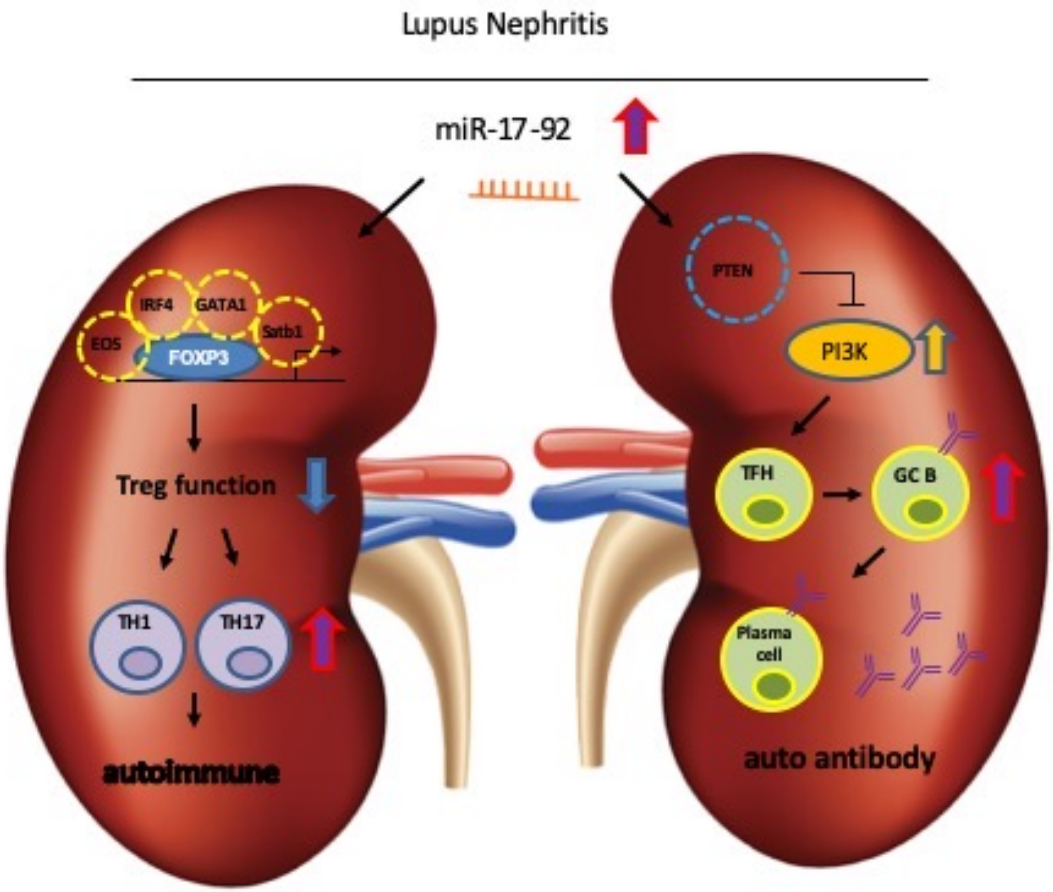


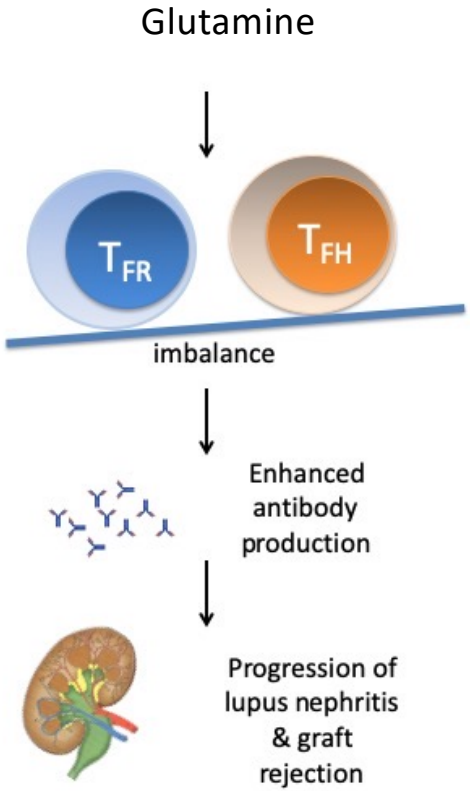
DON prevents IgG deposition in glomeruli and renal vasculatures in mice with early SLE





Summary


Lupus Nephritis
miR-17-92
IRF4
GATA1
EOS
FOXP3
Satb1
Treg function
TH1
TH17
autoimmune
PTEN
PI3K
TFH
GC B
Plasma cell
auto antibody


Glutamine
T_{FR}
T_{FH}
imbalance
Enhanced antibody production
Progression of lupus nephritis & graft rejection

APCN x TSN
2025

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