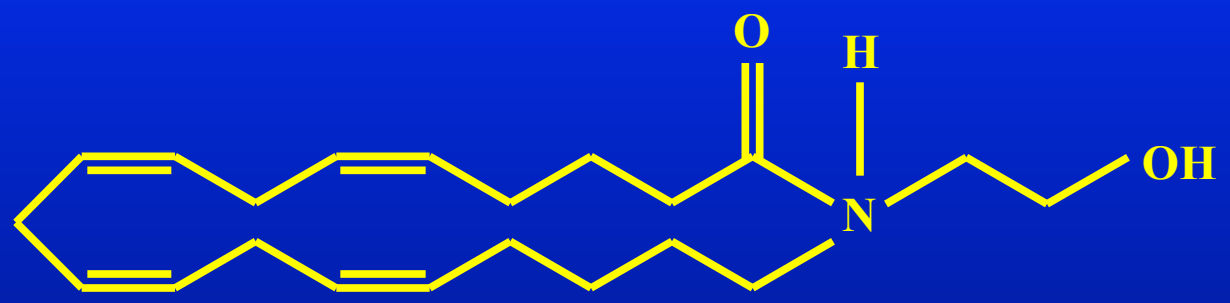
ENDOCANNABINOIDS



ANANDAMIDE

2-ARACHIDONOYL GLYCEROL (2-AG)

Physiological effects of cannabinoids

- Retrograde transmitter involved in synaptic plasticity (DSI, LTD, LTP)
- Analgesia, central and peripheral
- Anxiolytic RELAX
- Orexigenic EAT
- Mediates rewarding effects of drugs/alcohol DRINK
- Neuroprotection
- Motor suppression REST
- Seizure suppression
- Antinausea
- Sleep induction SLEEP
- Cardiovascular: hypotension, bradycardia
- ↑lipogenesis in liver and adipose tissue SAVE/STORE
- ↓ energy expenditure CONSERVE
- ↑ osteogenesis
- Hepatic fibrogenesis
- ↓oviductal transport, embryo implantation
- Antiinflammatory
- Tumor inhibitory
- ↓ GI motility
- ↓ intraocular pressure

Leptin-regulated endocannabinoids are involved in maintaining food intake

Vincenzo Di Marzo*, Sravan K. Goparaju†, Lei Wang†‡, Jie Liu†‡, Sándor Bátkai†‡, Zoltán Járai†, Filomena Fezza*, Grant I. Miura§, Richard D. Palmiter§, Takayuki Sugiura‖ & George Kunos†‡

NATURE | VOL 410 | 12 APRIL 2001 | www.nature.com

JAMA. 2006 Feb 15; 295(7):761-75.

Effect of Rimonabant, a Cannabinoid-1 Receptor Blocker, on Weight and Cardiometabolic Risk Factors in Overweight or Obese Patients

RIO-North America: a randomized controlled trial.

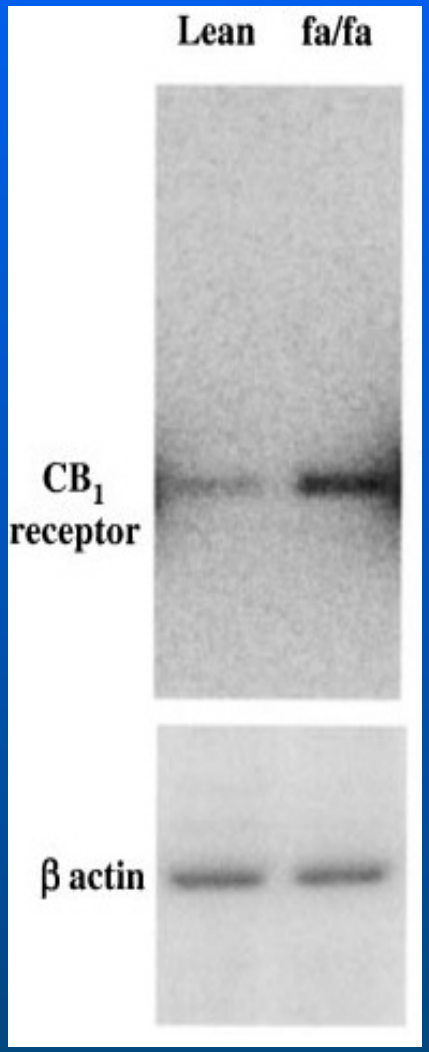
Pi-Sunyer FX[1], Aronne LJ, Heshmati HM, Devin J, Rosenstock J; RIO-North America Study Group

Metabolic Effects of Peripheral CB_1R Activation

- Adipose tissue: ↑ lipogenesis, ↓ fat oxidation → obesity (Cota et al., JCI 2003)
- Liver: ↑ glucose production → insulin resistance; ↑ lipogenesis, ER stress → fatty liver (Osei-Hyiaman et al., JCI 2005; 2008)
- Muscle:↓glucose uptake → insulin resistance (Liu et al., Int J Obes 2005)
- Pancreas (beta cells): ↑ beta cell apoptosis (Kim et al., Sci Signal 2012)
- Macrophages, podocytes: see later in this talk

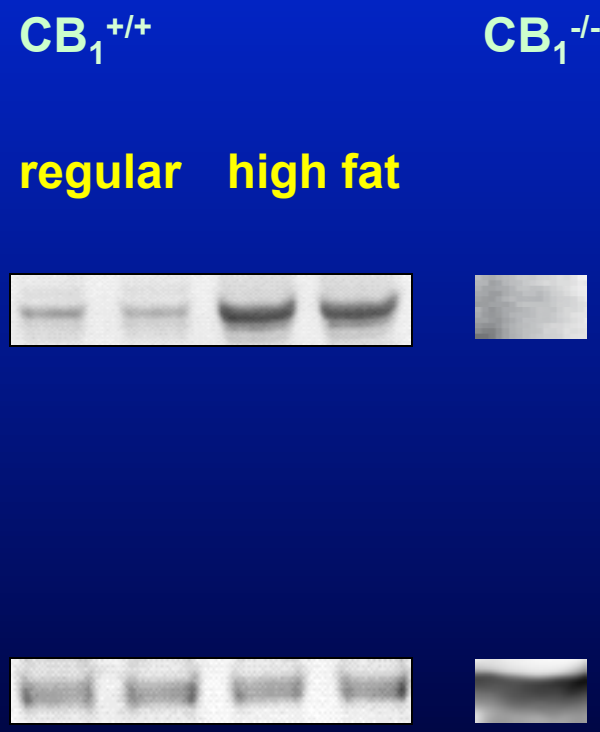
Upregulation of CB_1R in obesity

Rat Adipocyte



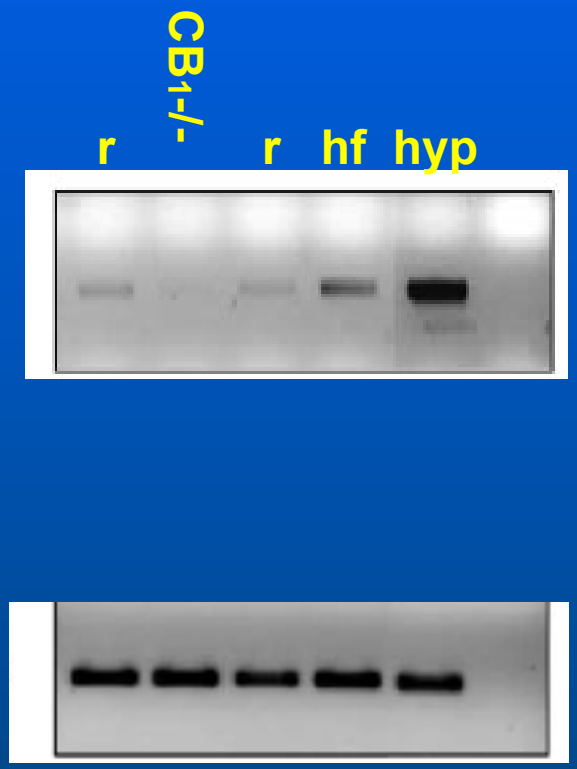
Bensaid M et al. *Mol Pharmacol*. 2003;63:908-914.

Mouse hepatocytes



Osei-Hyiaman D et al. *J Clin Invest*. 2005;115:1298-1305.

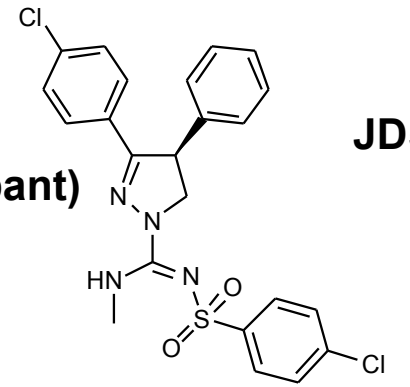
Mouse Soleus Muscle



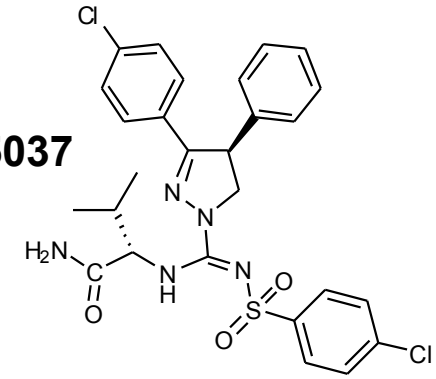
Pagotto U et al. *Endocr Rev*. 2006;27:73-100.

High CB_1 affinity and inverse agonist property of novel peripheral CB_1 antagonist (JD5037) and its brain-penetrant parent compound (SLV319)

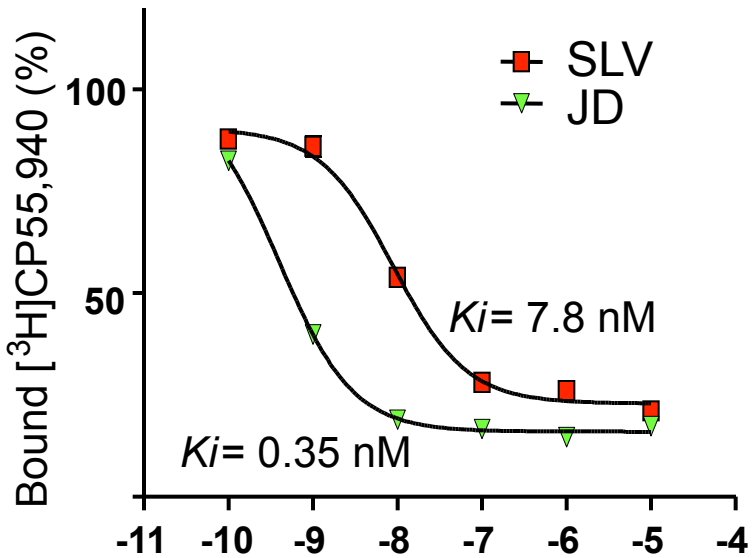
SLV319 (ibipinabant)

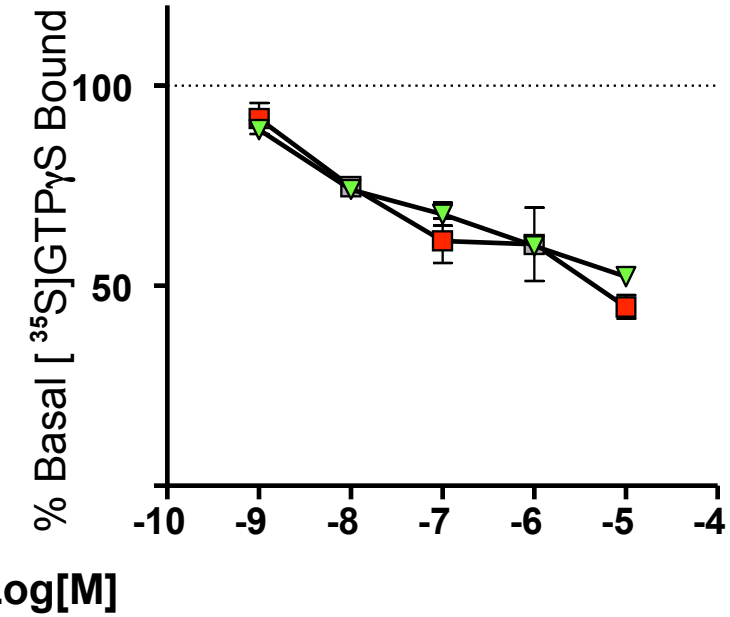


JD5037



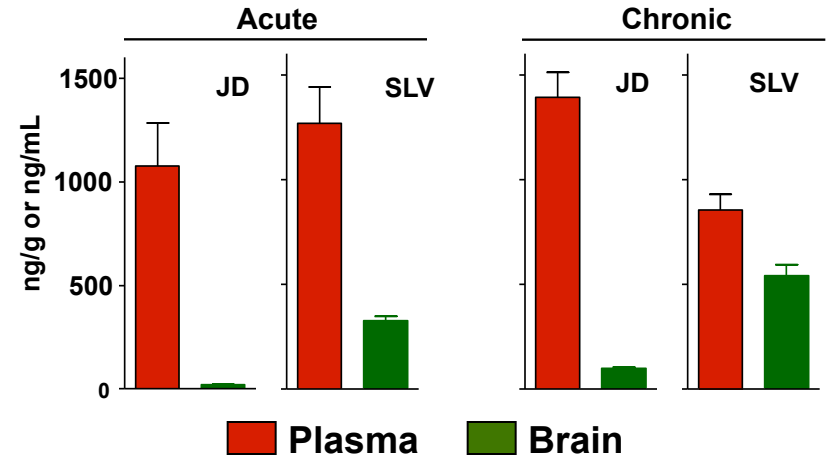
Properties	Preferred range for CNS	Rimonabant	SLV-319	JD-5037
cLogP	2-4	6.28	5.88	6.00
MW	<450	464	487	572
PSA (A^2)	<70	50	74	117
HBD	0-1	1	1	3

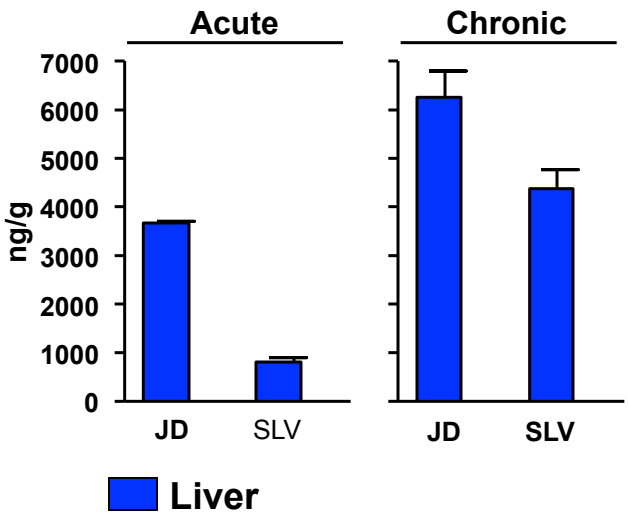


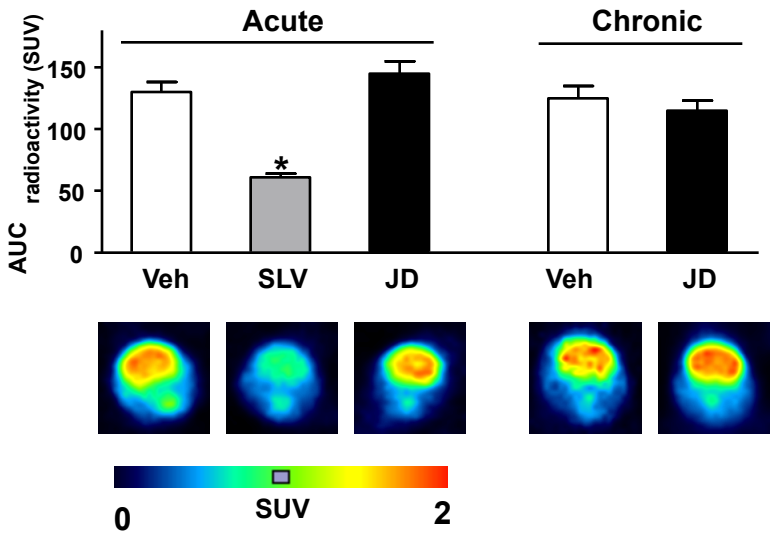


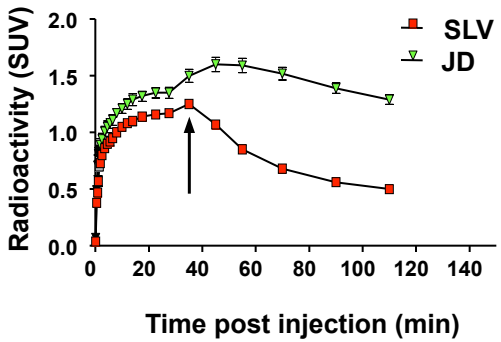
Tam et al., *Cell Met 16:167-79, 2012*

Minimal brain penetrance and brain CB_1 occupancy by JD5037



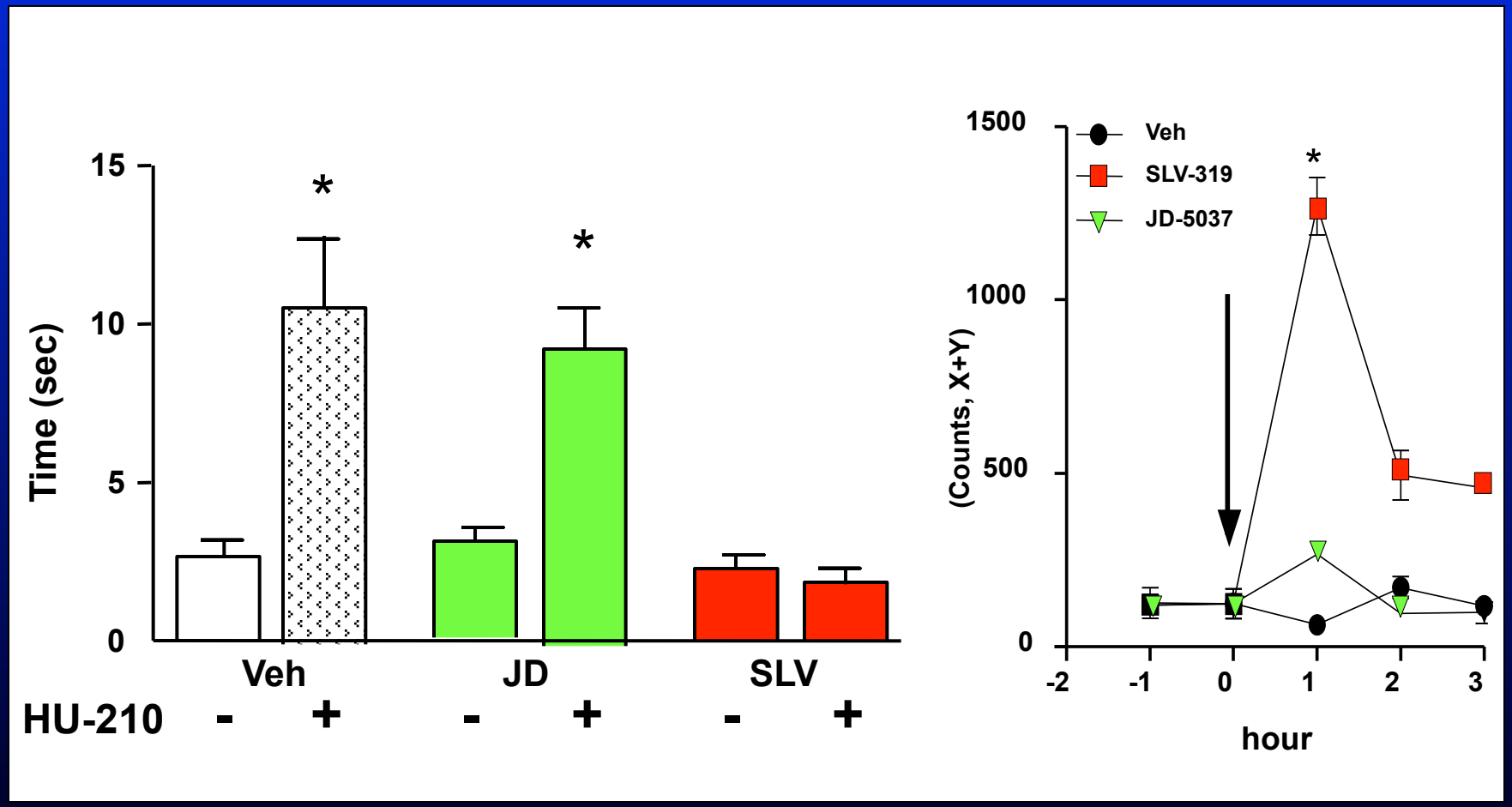






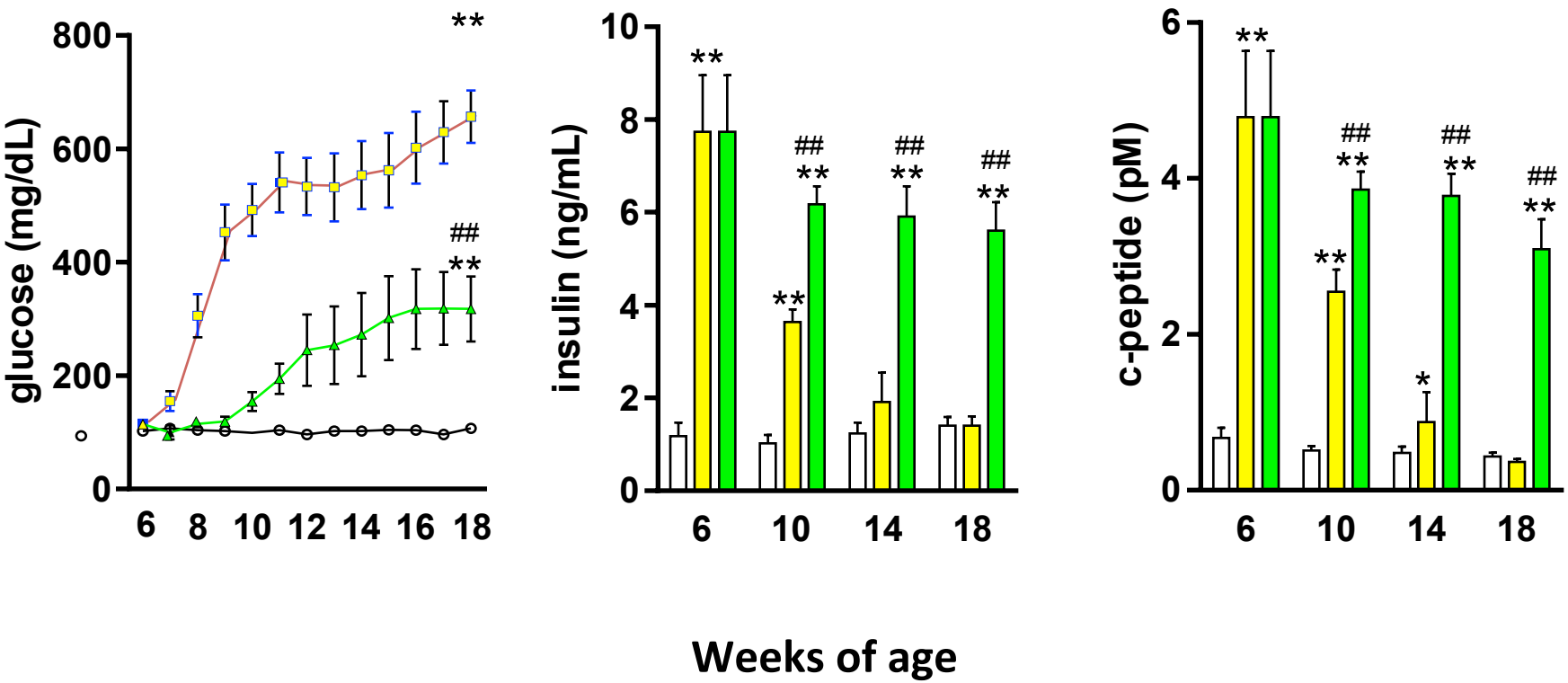
Tam et al., *Cell Met 16:167-79, 2012*

SLV319 but not JD5037 blocks CB_1-mediated catalepsy and increases ambulatory activity



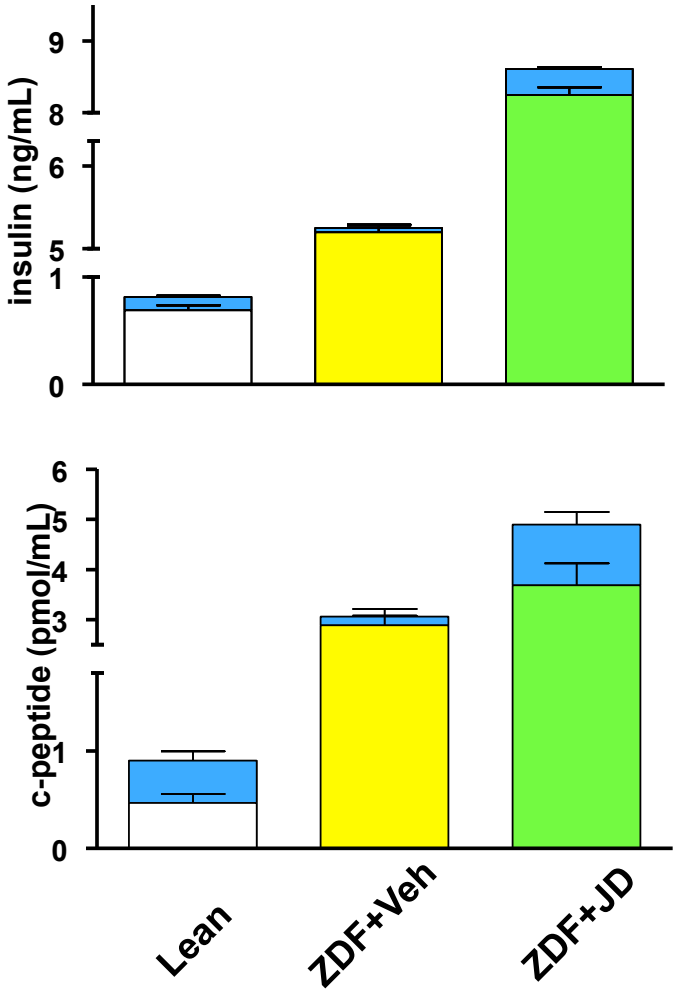
Tam et al., *Cell Met 16:167-79*, 2012.

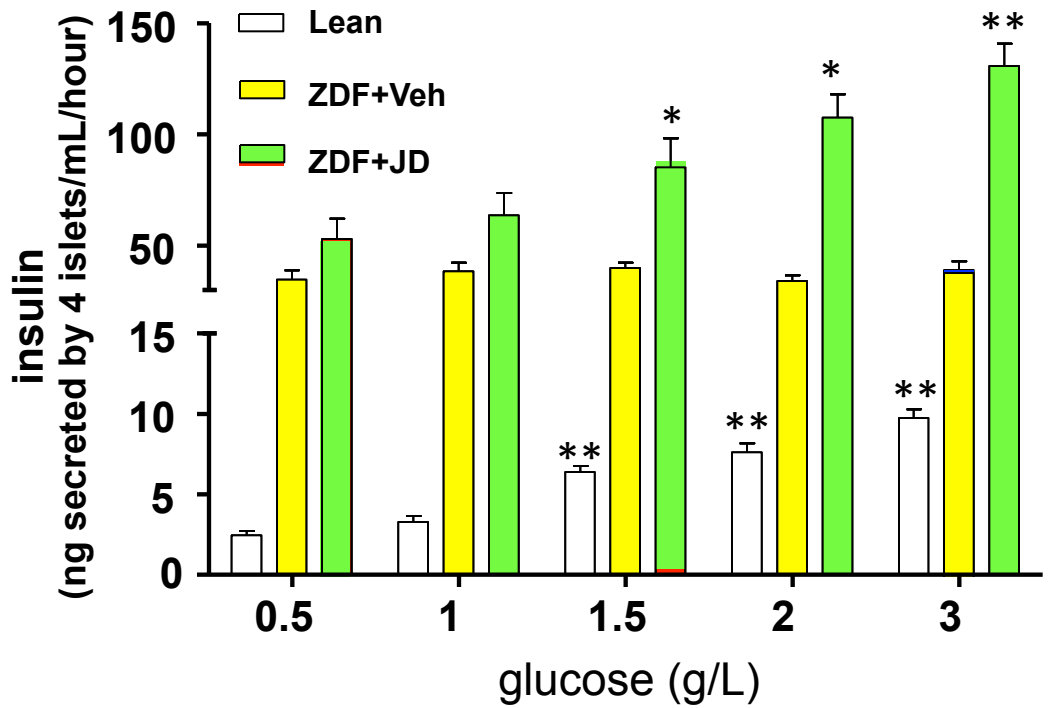
Chronic JD5037 treatment delays the onset and attenuates diabetes and β-cell loss



Jourdan et al. *Nat Med* 19:1132, 2013

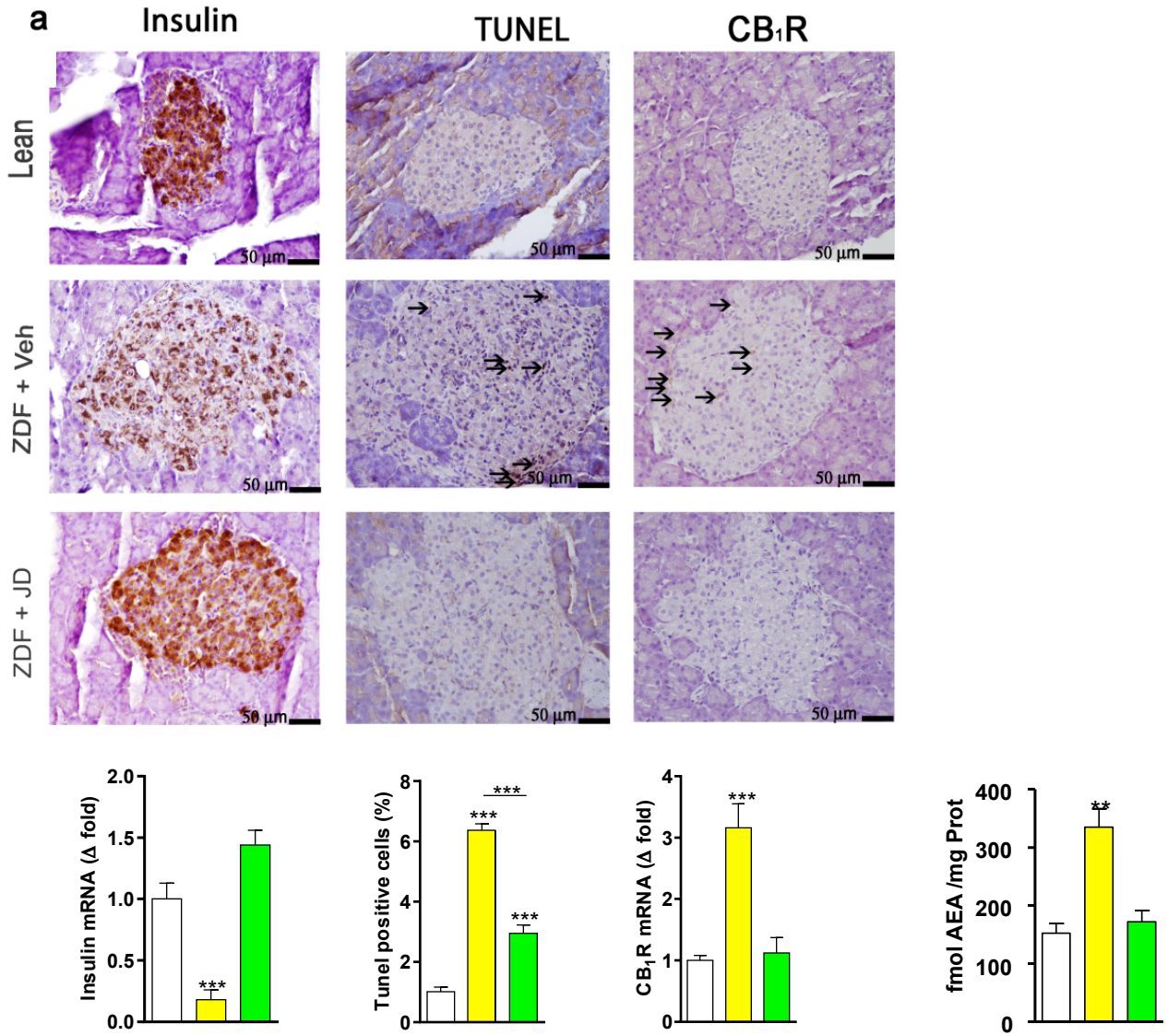
JD-5037 treatment of ZDF rats restores glucose-induced insulin release in vivo (left) and in vitro (right)





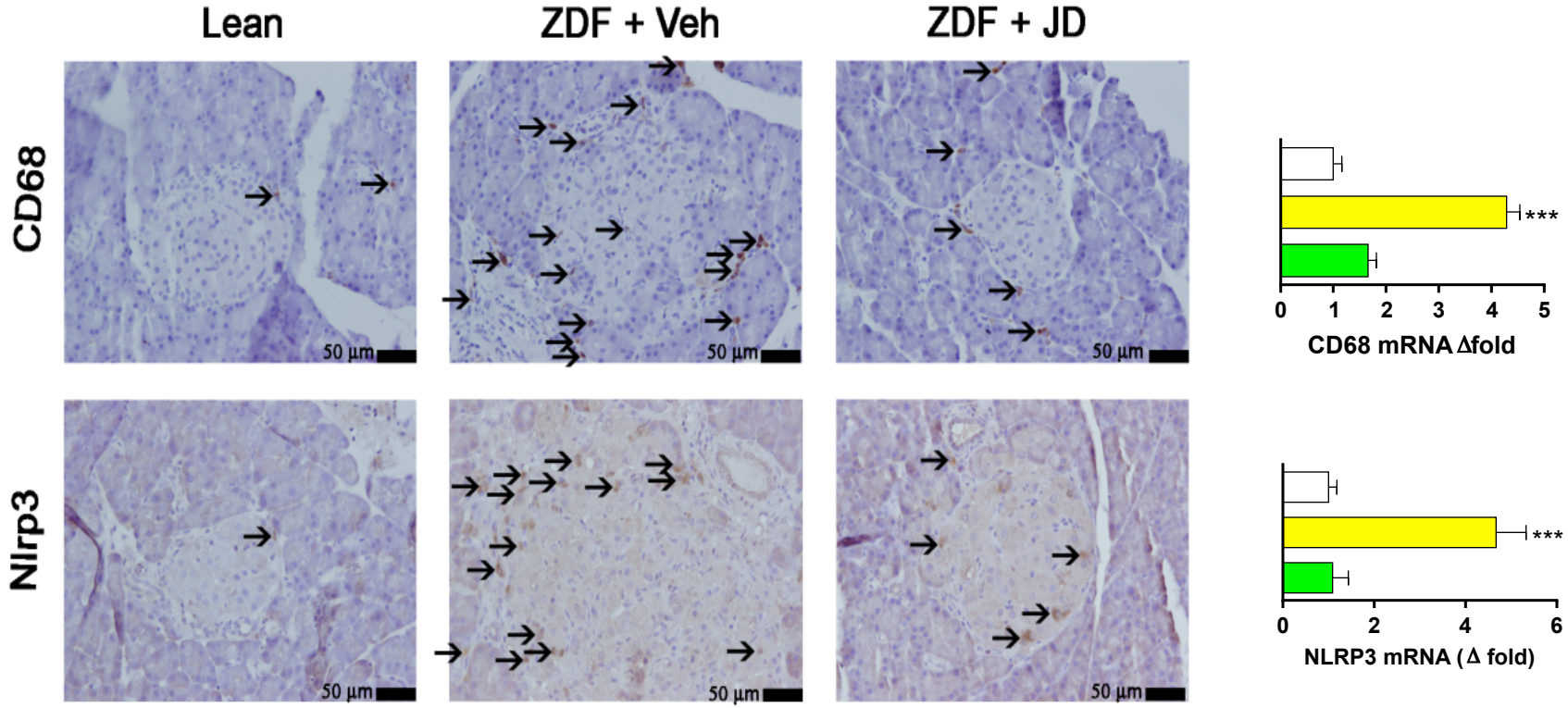
Jourdan et al. *Nat Med* 19:1132, 2013

β-Cell loss in ZDF islets is reversed by CB_1R blockade



Jourdan et al. *Nat Med* 19:1132, 2013

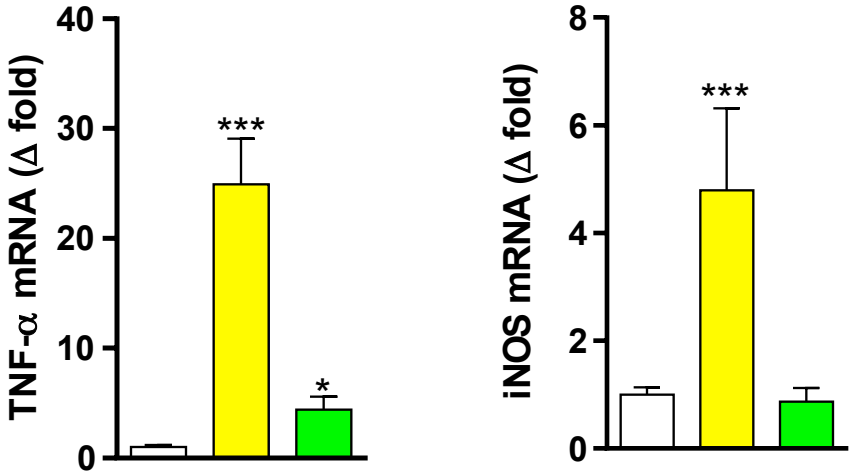
Islet infiltration by proinflammatory macrophages is reversed by JD5037 treatment



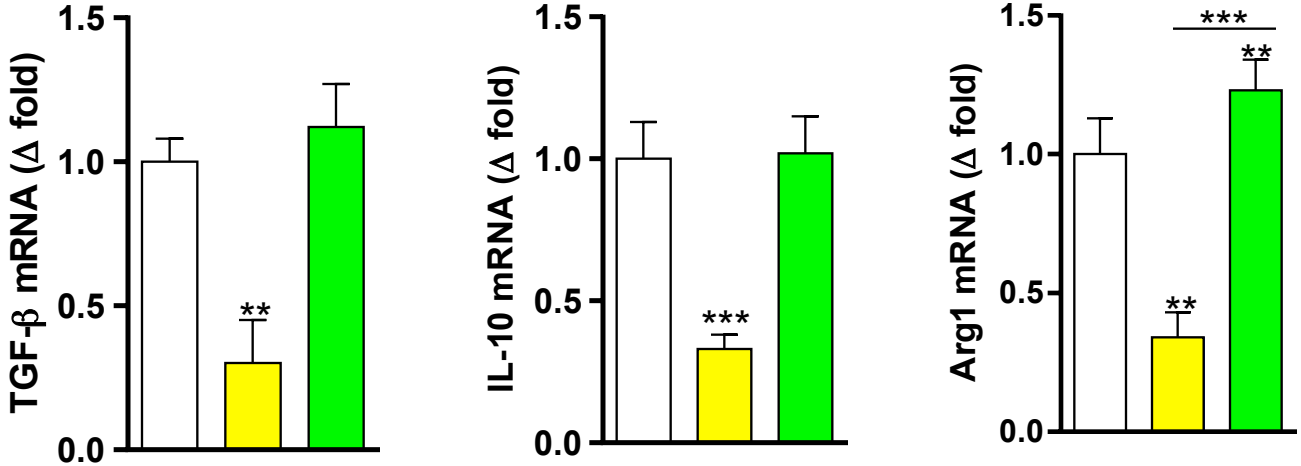
Jourdan et al. *Nat Med* 19:1132, 2013

M2→M1 shift in ZDF islets is reversed by chronic CB_1R blockade

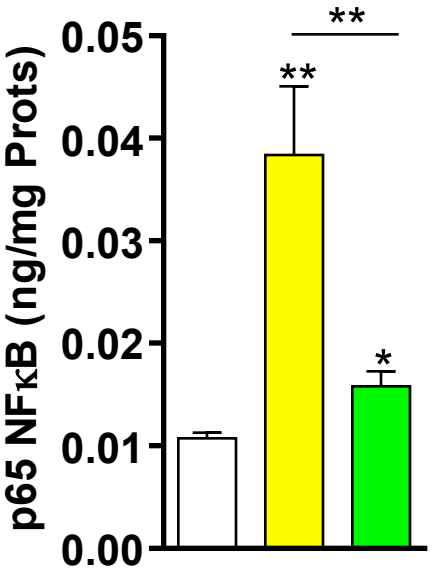
M1:

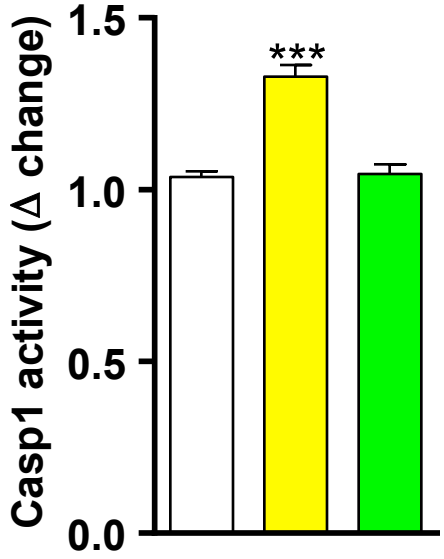


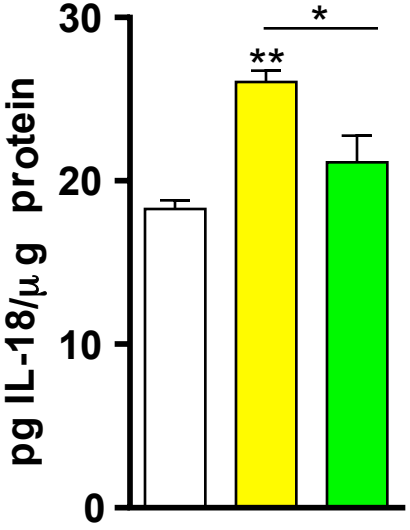
M2:

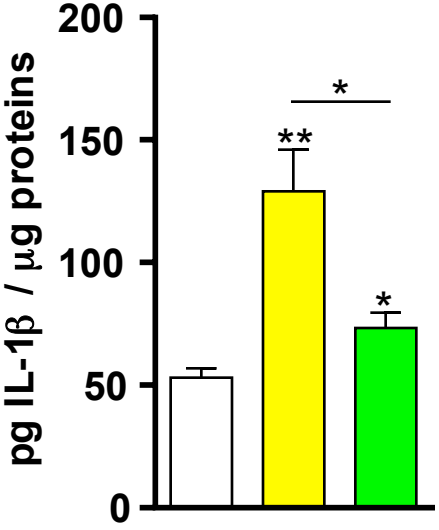


Inflammasome activation in ZDF islets is reversed by CB_1R blockade

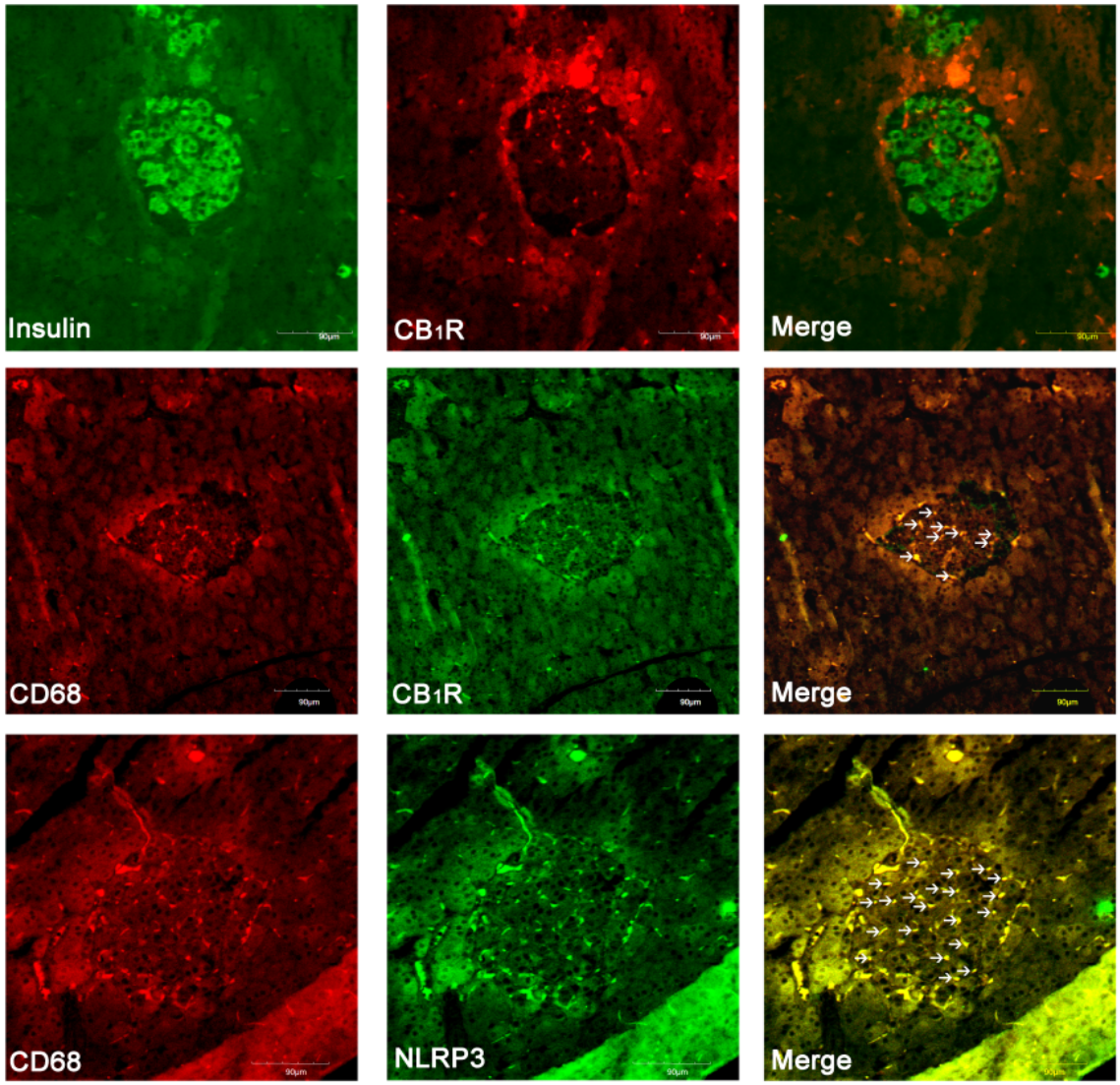






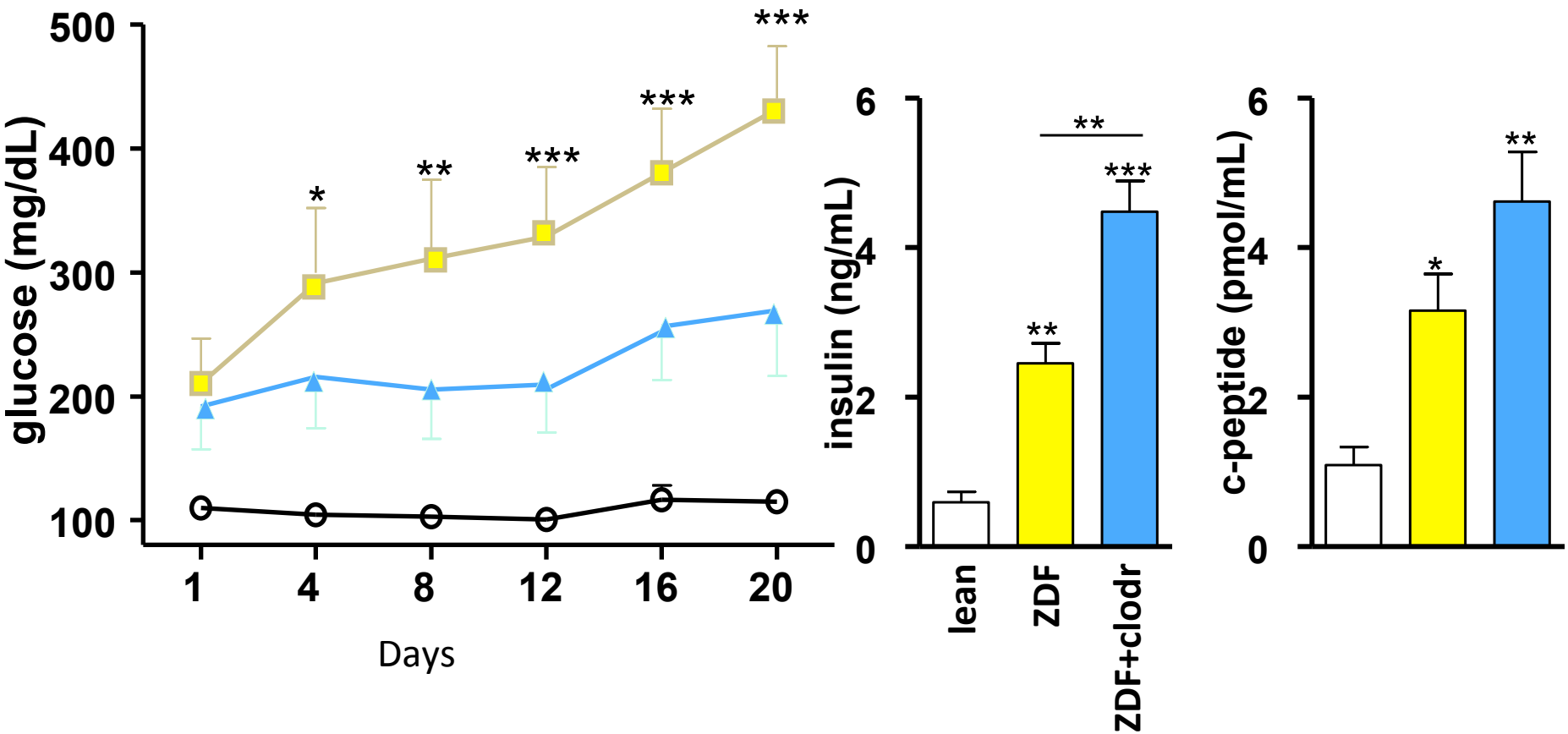


CB_1R and Nlrp3 colocalize with macrophages, not β-cells in ZDF islets



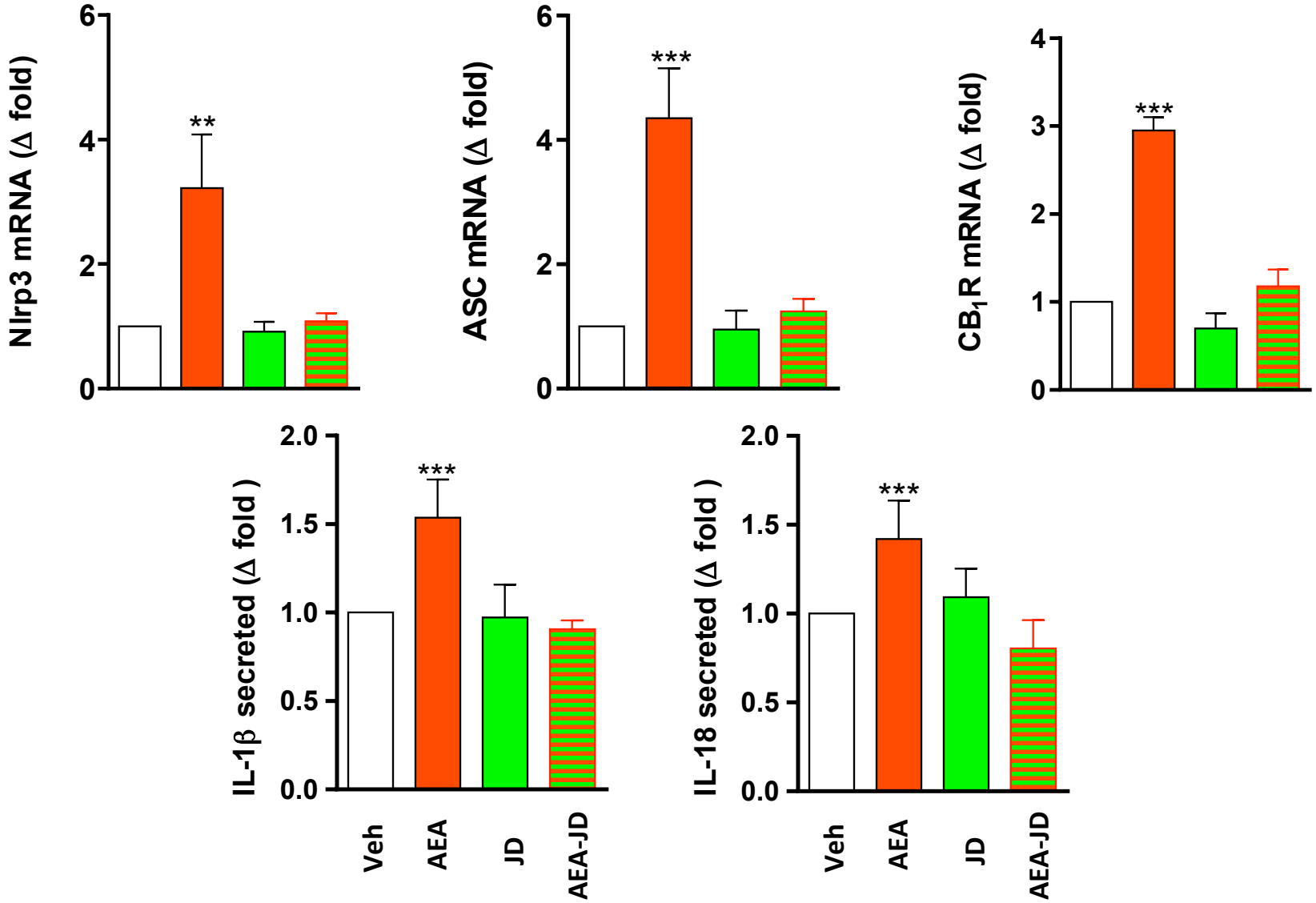
Jourdan et al. *Nat Med* 19:1132, 2013

Macrophage depletion reverses hyperglycemia and β-cell loss in ZDF rats

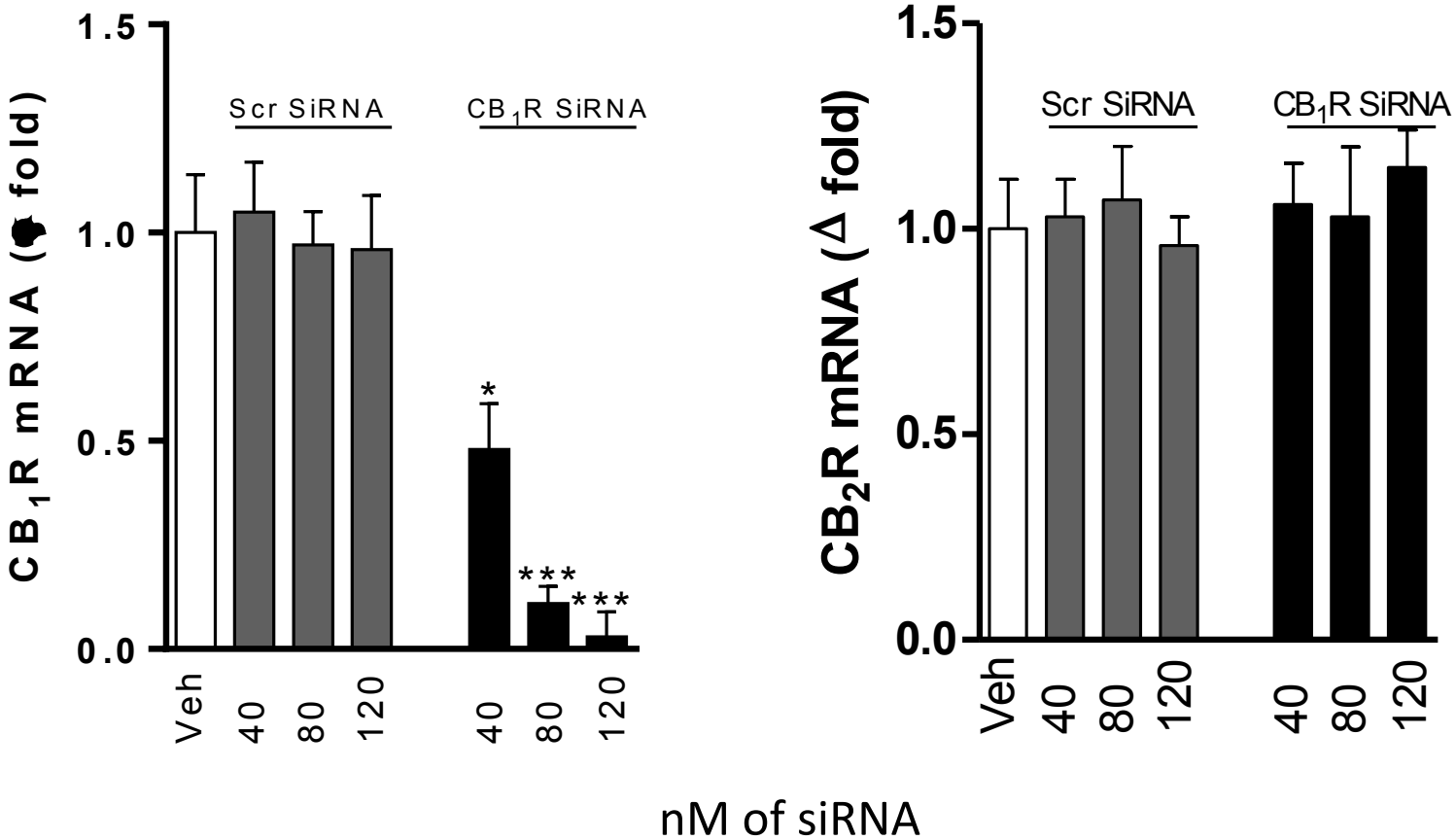


Jourdan et al. *Nat Med* 19:1132, 2013

AEA activation of NLRP3 inflammasome in human macrophages is CB_1R dependent

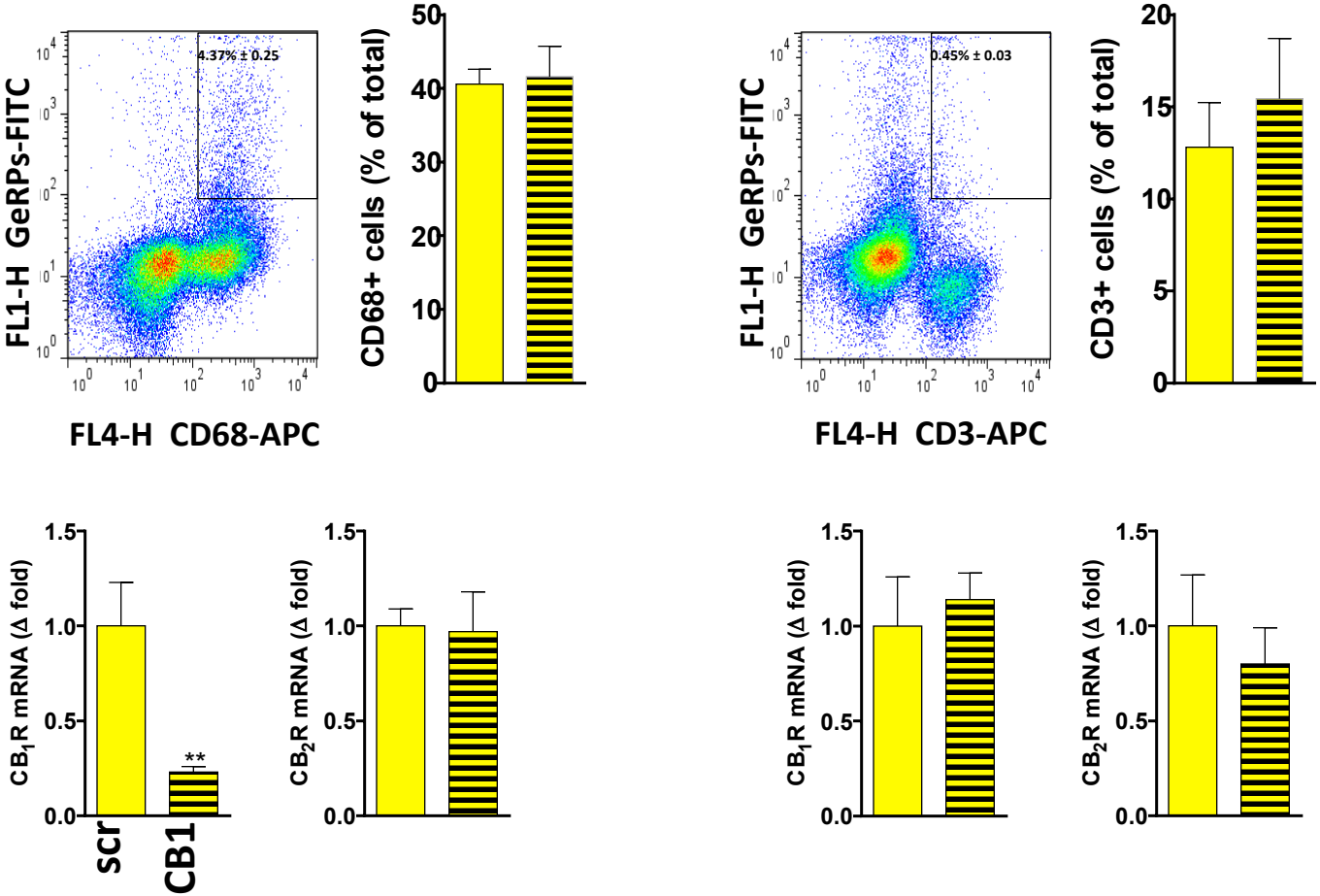


siRNA knockdown of *Cnr1* in rat PECs



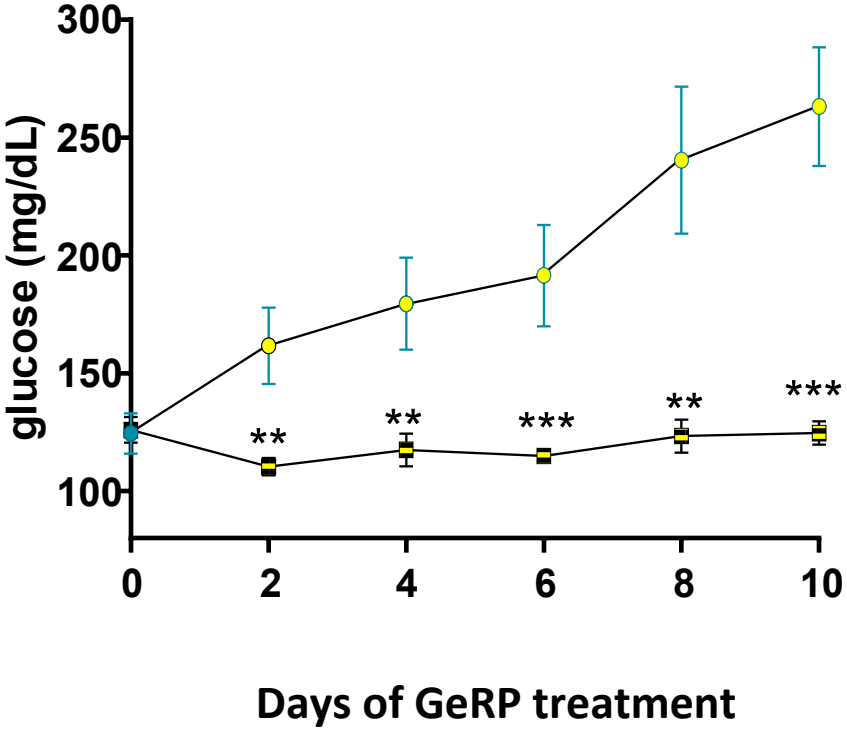
Jourdan et al. *Nat Med* 19:1132, 2013

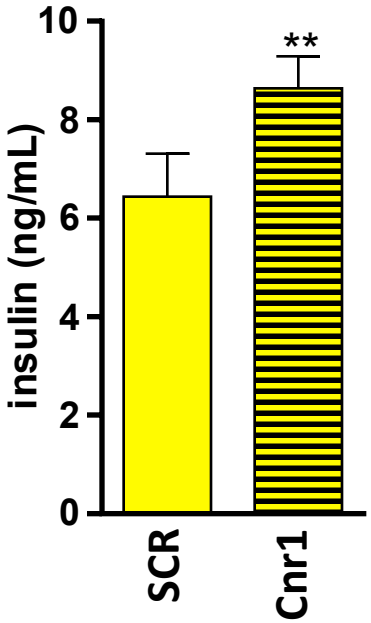
Selective knockdown of *Cnr1* in CD68$^+$ but not in CD3$^+$ PECs

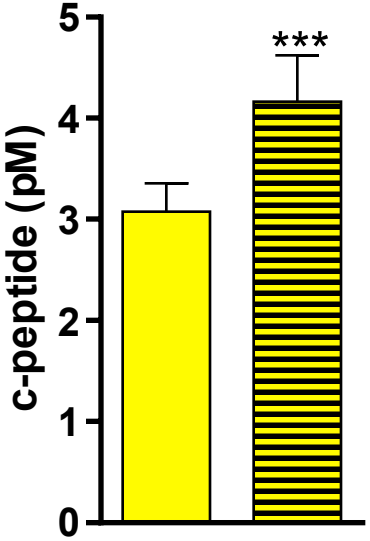


Jourdan et al. *Nat Med* 19:1132, 2013

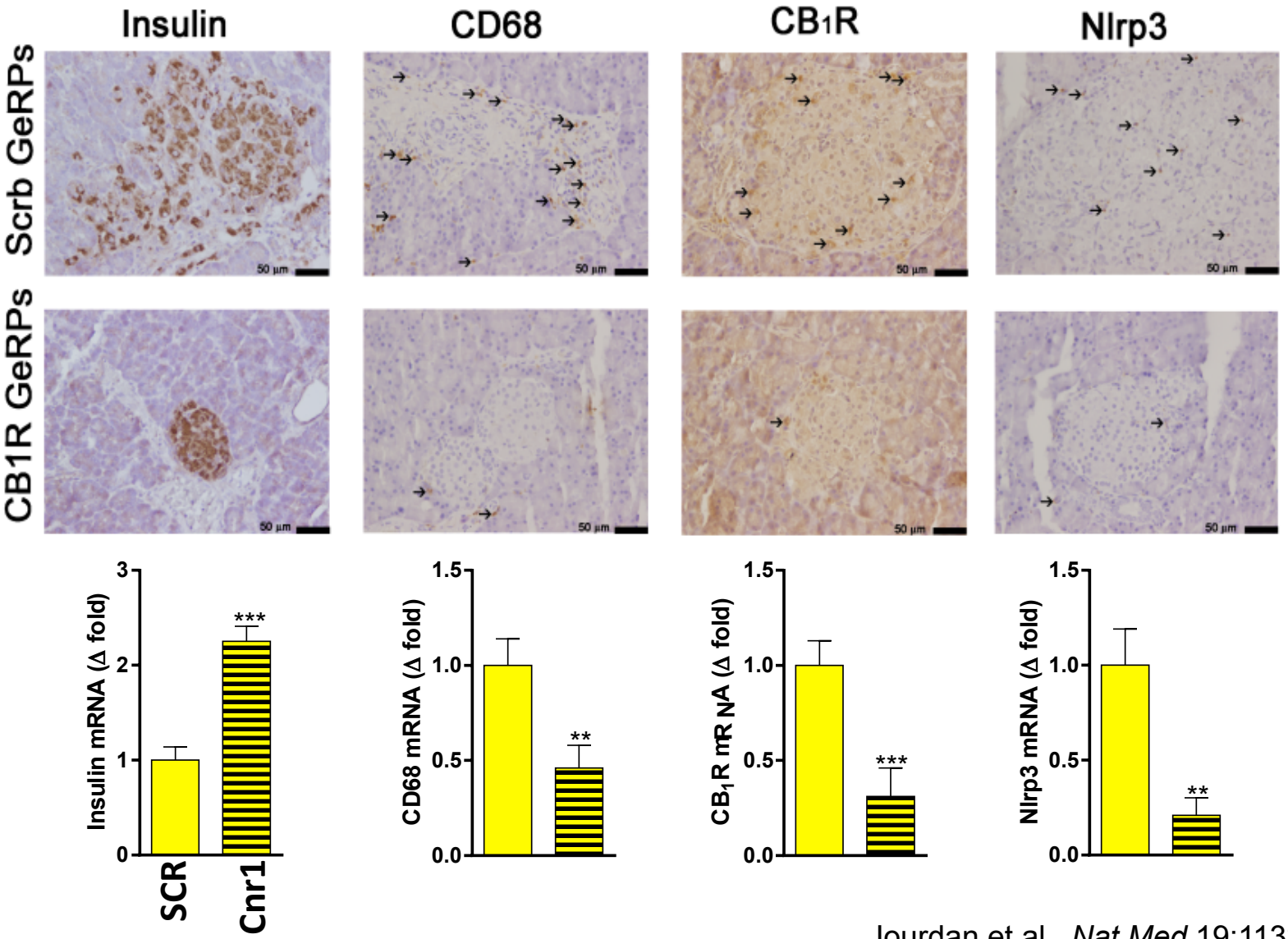
Knockdown of Mø *Cnr1* prevents hyperglycemia and β-cell loss







Effects of Mø *Cnr1* knockdown on ZDF islets

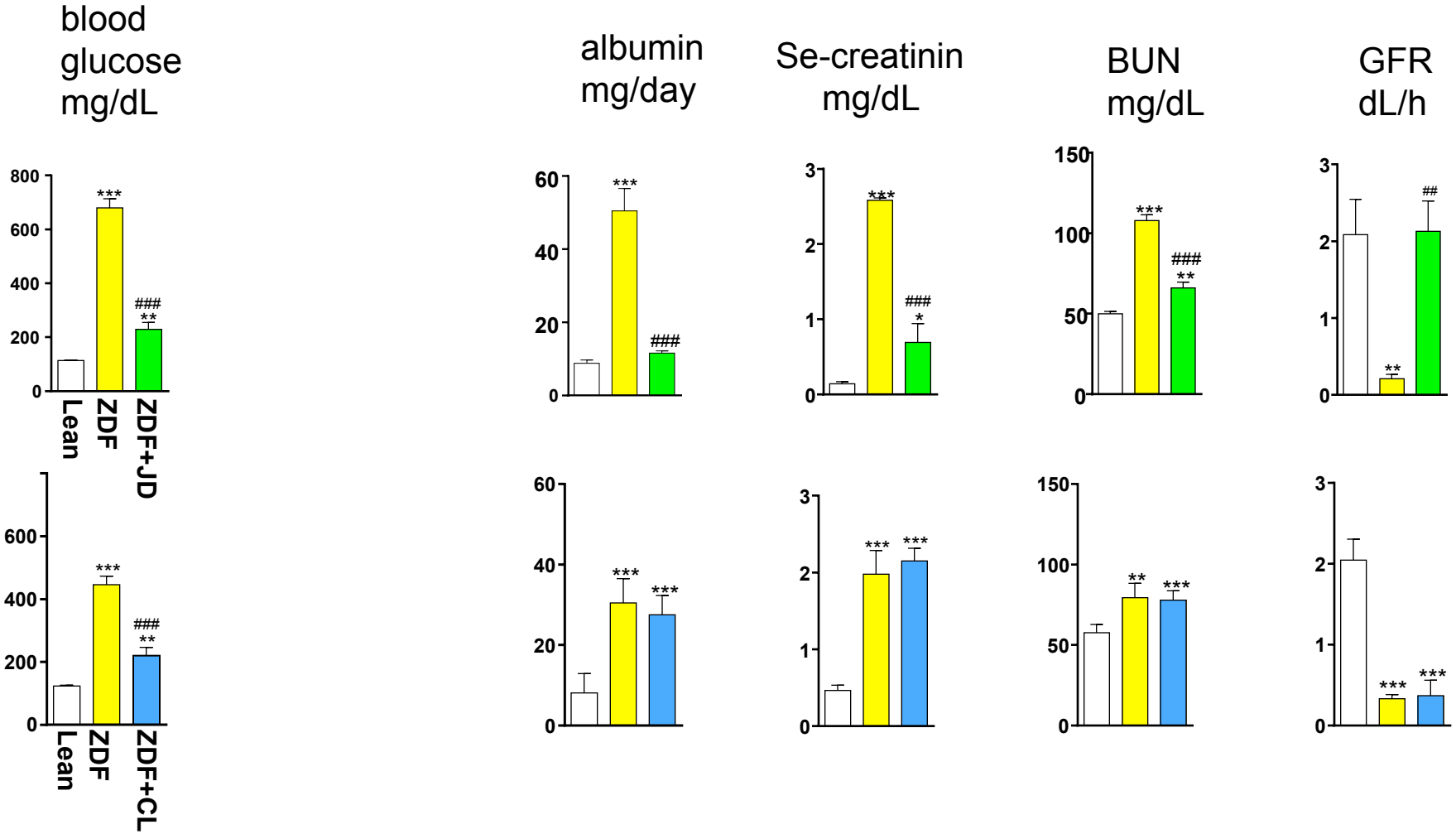


Jourdan et al., *Nat Med* 19:1132, 2013.

Diabetic Nephropathy

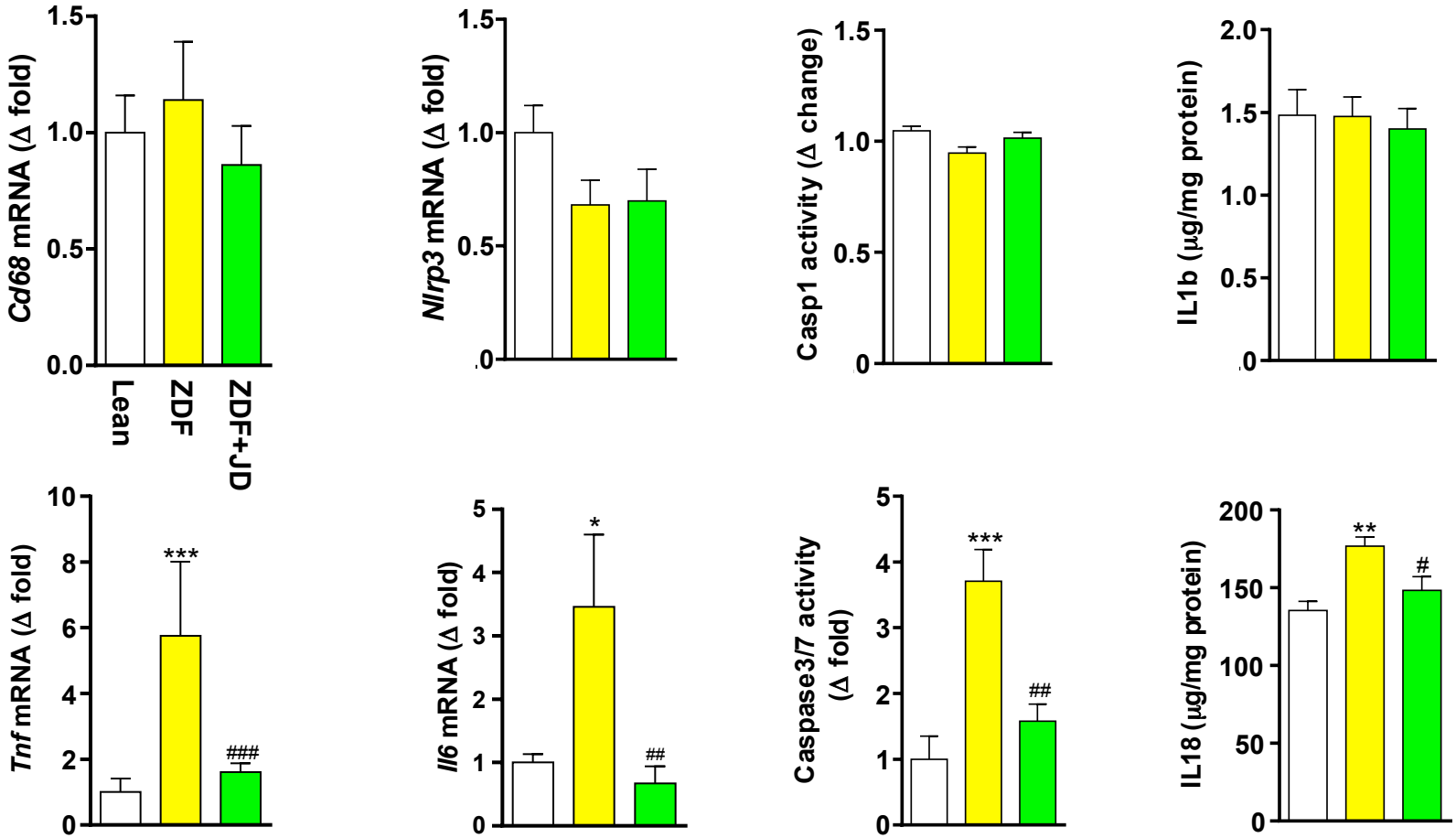
- **Primarily a glomerular disease;**
- **The most common cause of end-stage renal disease;**
- **Injury of podocytes (specialized vascular epithelial cells that maintain the integrity of the glomerular filtration apparatus and regulate glomerular filtration rate) is a key pathogenic factor in diabetic glomerulopathy;**
- **Angiotensin II and hyperglycemia are the two main drivers of diabetic glomerulopathy;**

CB_1R blockade, but not macrophage depletion, prevents nephropathy



Jourdan et al., PNAS 2014

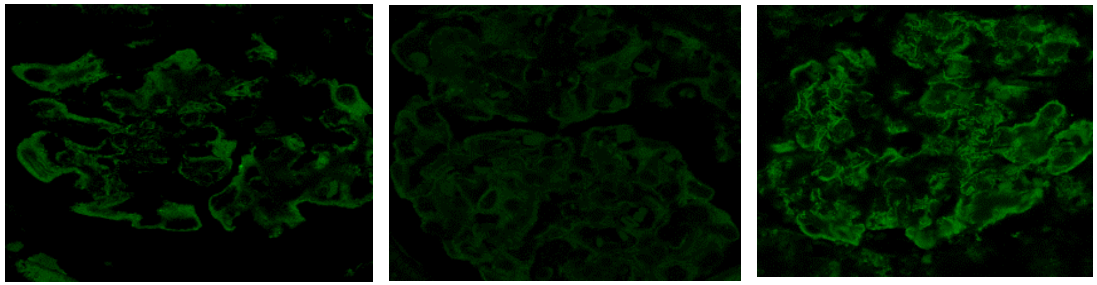
No evidence for macrophage infiltration or Nlrp3 activation in ZDF kidney

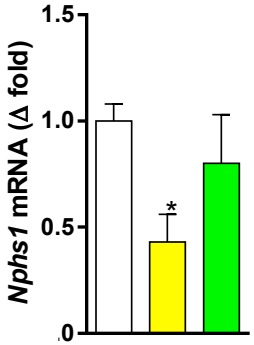


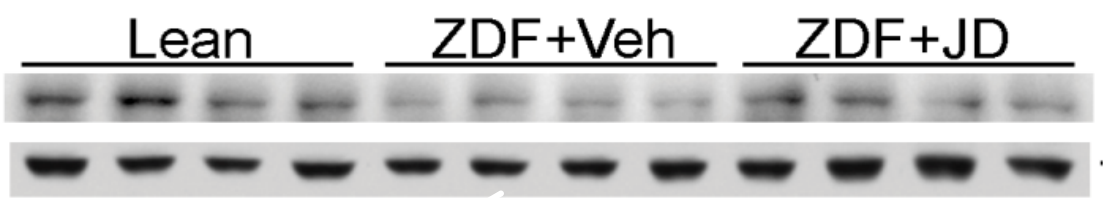
Jourdan et al. PNAS 2014

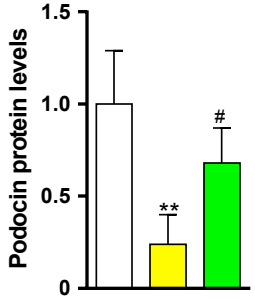
Reversal of podocyte loss and increased CB_1R expression in ZDF rats by CB_1R blockade

Podocin IHC

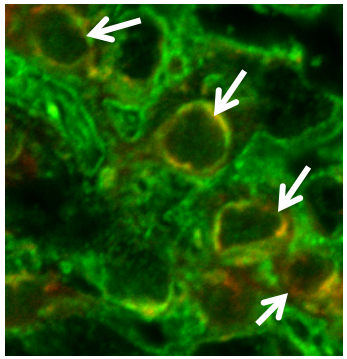




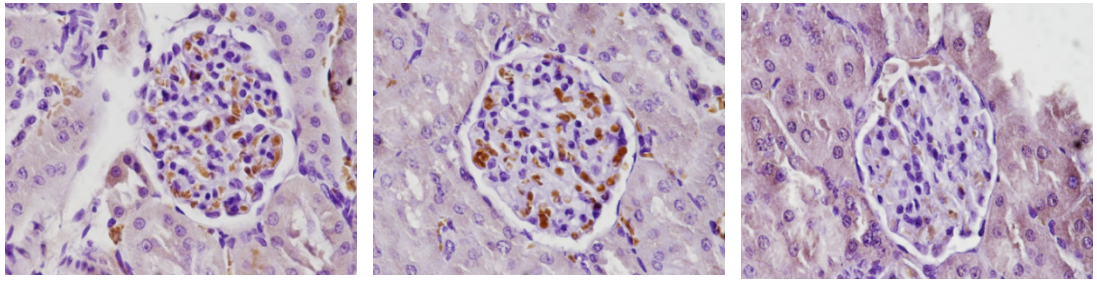


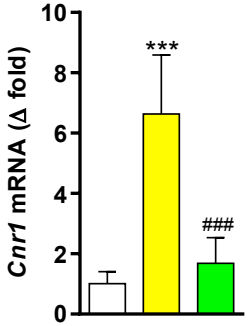


Podocin/CB_1R



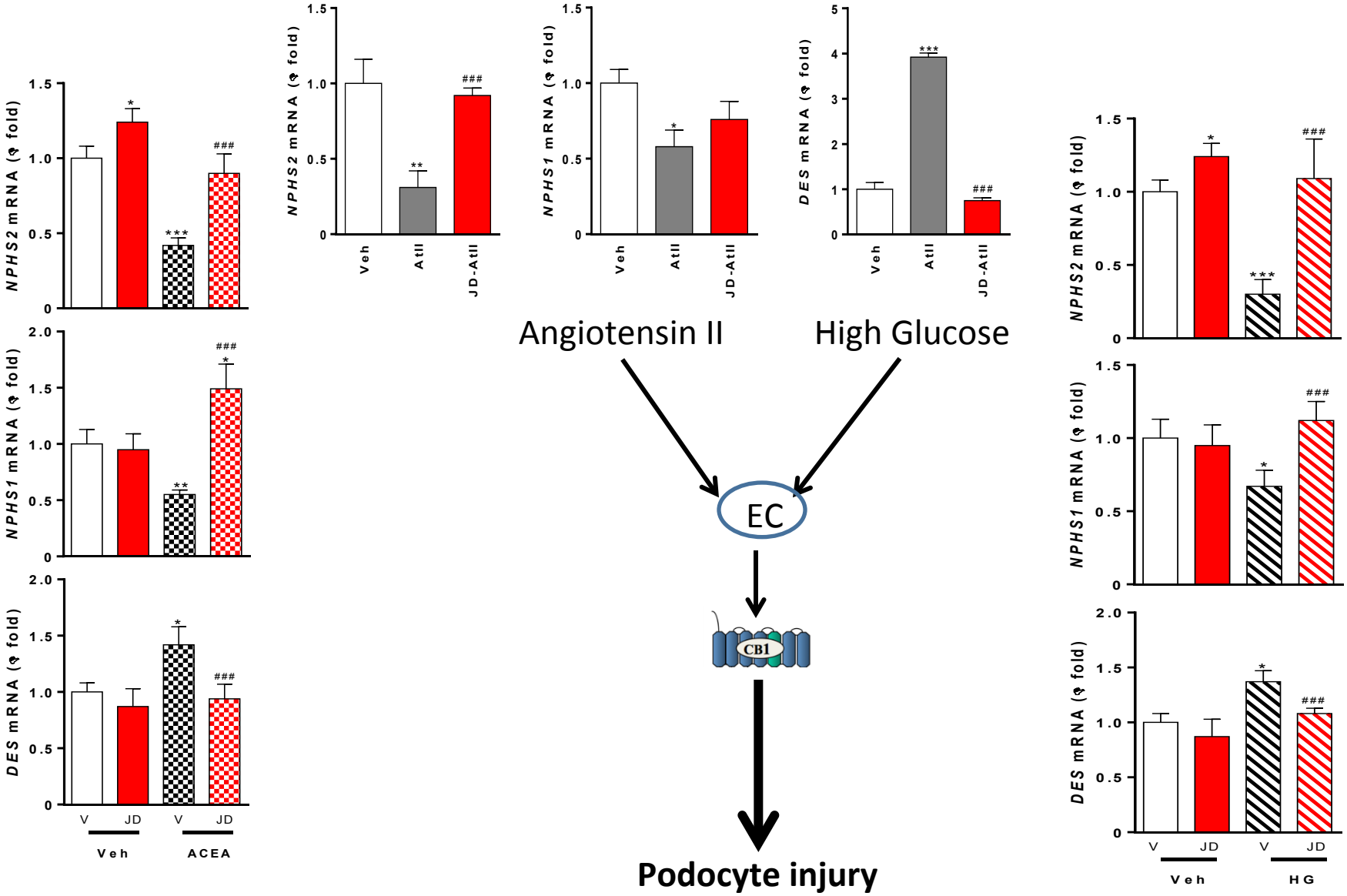
CB1R IHC





Jourdan et al., PNAS 2014

Angiotensin II or high glucose-induced podocyte injury is CB1R-dependent.



Conclusions

- Increased CB_1R signaling in ZDF macrophages promotes their transmigration into islets and activates the NIrp3/ASC inflammasome
- β-Cell loss in ZDF rats is due to the paracrine, proapoptotic action of macrophage-derived IL-1β and IL-18
- Peripheral CB_1R blockade delays the progression of T2DM and protects β-cells by preventing inflammasome activation and islet infiltration by macrophages

Conclusions (cont'd)

- Diabetic nephropathy can develop in the absence of hyperglycemia or macrophage infiltration, is associated with increased CB_1R expression in glomeruli, and is prevented by peripheral CB_1R blockade
- Both high glucose and AtII induce podocyte damage and upregulate CB_1R expression in podocytes, and the effects of both are inhibited by CB_1R blockade.
- Increased CB_1R signaling in podocytes may function as a final common pathway in diabetic glomerulopathy
- Peripheral CB_1R antagonists have therapeutic potential in T2DM and its complications.

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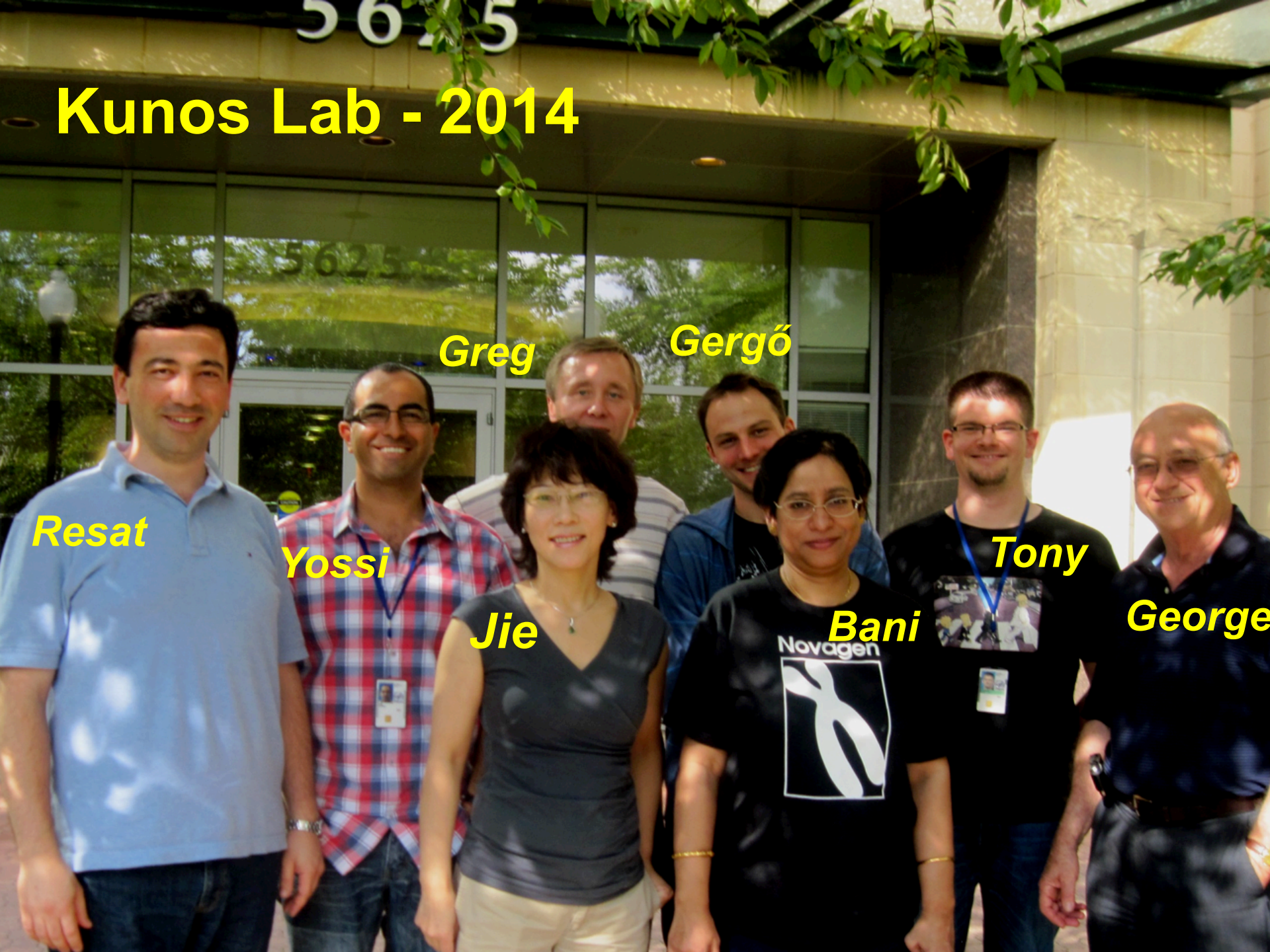

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Adeline Bertola