Role of Leptin and Other Adipokines in HIV Infection and HIV-related Obesity

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Division of Infectious Diseases

National Institutes of Health
Obesity and Fat Metabolism in HIV-infected Individuals Workshop

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Disclosures

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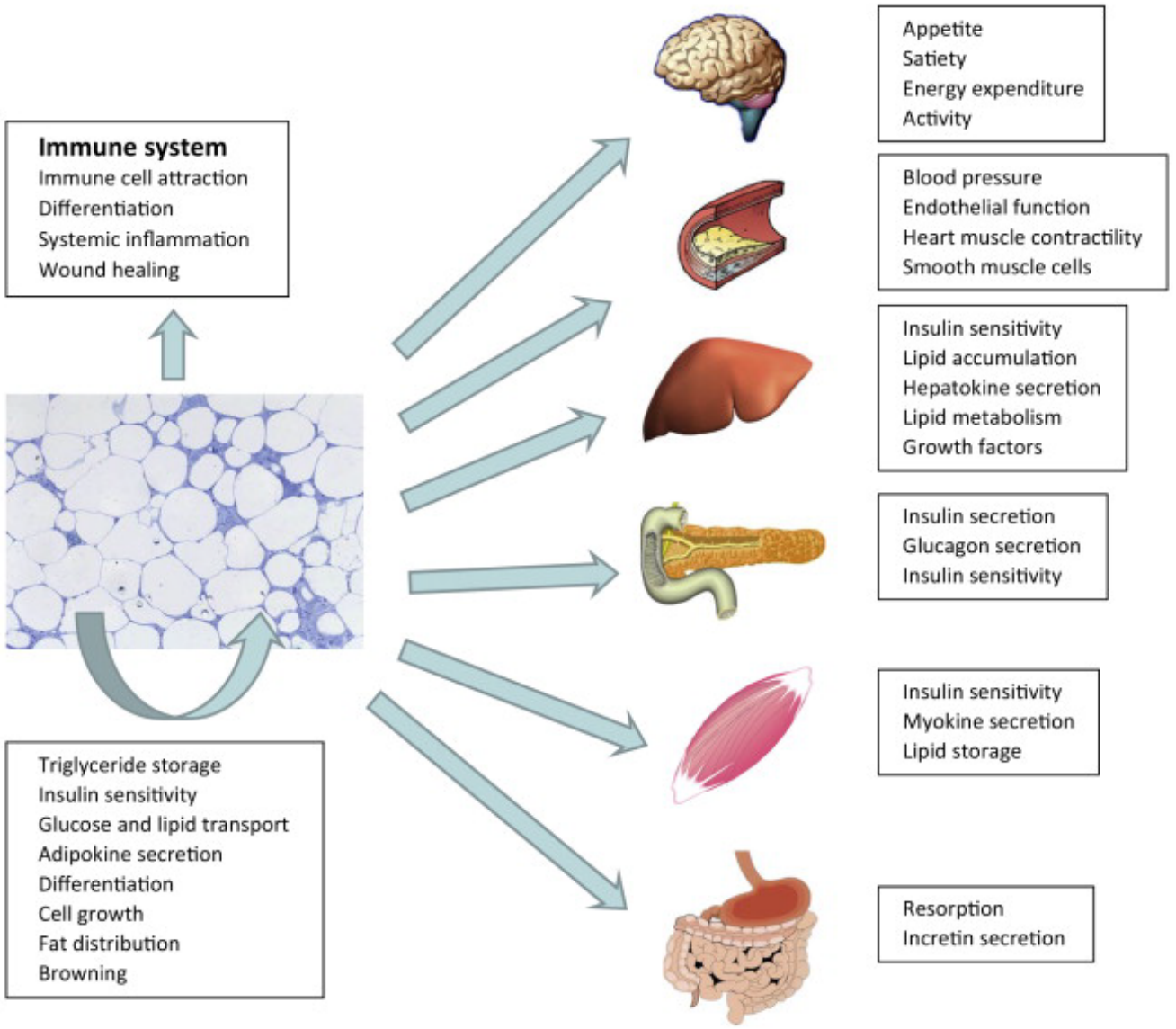
Adipokines: peptides signaling the energy storage status of adipose tissue to brain, and other organs.

Leptin
Adiponectin
Visfatin/Nampt/PBEF
Vaspin
RBP4
FGF21
BMPs
Nesfatin-1
Cathepsins
Apelin
Omentin
Lipocalin
and hundreds more

Adipokines inform the body that sufficient energy is available to mount a given response, or that limited energy availability should constrain the response



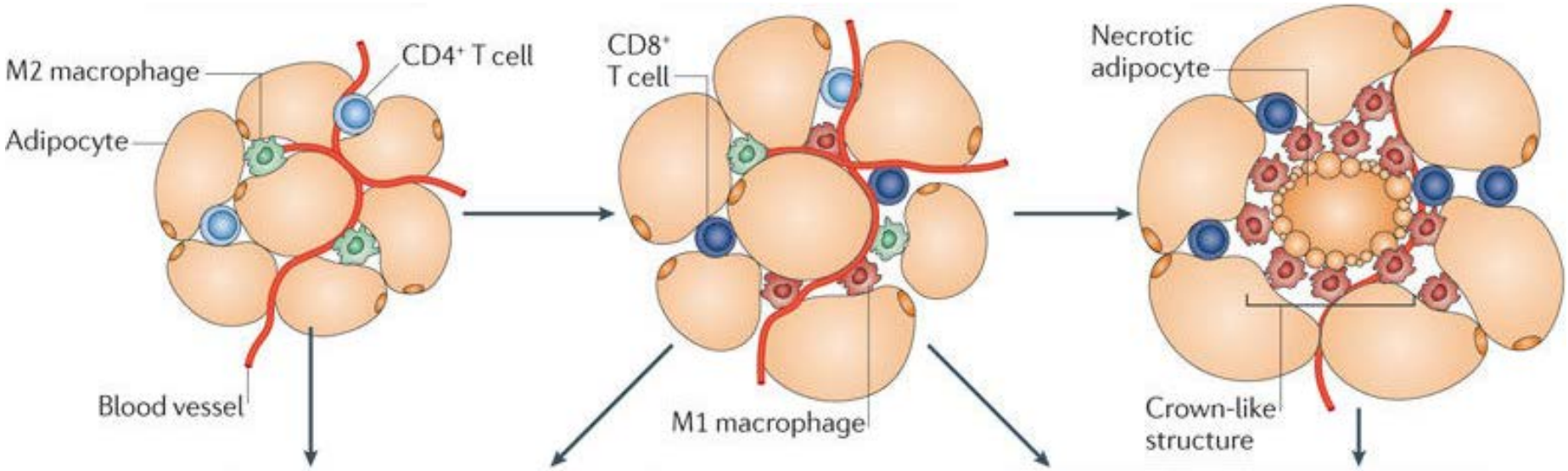
Fasshauer M & Bluher M. *Trends in Pharm. Sci*. 2015.

Relative adipokine production shifts with progressive obesity

Lean
Inflammation controlled
Metabolic function intact

Obese 'Healthy'
↑ Inflammation
↓ Metabolic function

Obese 'Unhealthy'
↑↑ Inflammation
↓↓ Metabolic function



'Lean adipokines'
- Adiponectin
- Secreted frizzled-related protein 5 (Sfrp5)

'Obese adipokines'
- Leptin
- Retinol binding protein-4 (RBP4)
- Resistin

Adipocyte hypertrophy
- IL-6
- TNF-α
- MCP-1

Ouchi N, *et al. Nat. Rev. Imm*. 2011.

Adiponectin and leptin balance central to regulating multiple biological processes

Adiponectin

- **Increases in lean states, falls precipitously with visceral obesity (a *Hormone of Starvation*)**
- **Stimulates food intake and suppresses energy expenditure**
- **Sensitizes liver and muscle to insulin**
- **Anti-atherogenic (reduces endothelial activation, prevents foam cell formation and plaque T cell entry)**
- **Adipose paracrine activity:**
  - Promotes M2 macrophage phenotype, clearance of apoptotic debris
  - Reduces T cell infiltration, activation
  - Promotes adipocyte hyperplasia

Leptin

- **Circulates in proportion to fat mass (a *Hormone of Plenty*)**
- **Servers as indicator of global energy stores**
- **Reduces appetite and increases activity**
- **Receptors are widely expressed (CNS, immune, CV, hepatic, GI and other tissues) – A *rheostat* for many processes**
- **Broad immune effects:**
  - Innate immune cell proliferation/activation
  - T and B cell proliferation and survival
  - T_H1 polarization

Tilg H and Moschen A, *Nature Rev*, 2006; Ohashi K, *et al. Trends in Endo and Met,* 2014.

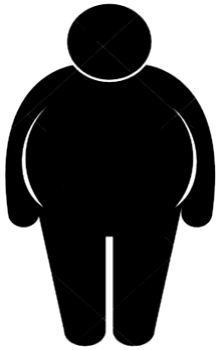
Adiponectin and leptin: a delicate balance regulating immune activity

Low leptin / high adiponectin
- Malnutrition
- Leptin and leptin receptor deficits

Reduced response to antigen, proliferation, and activation to conserve energy

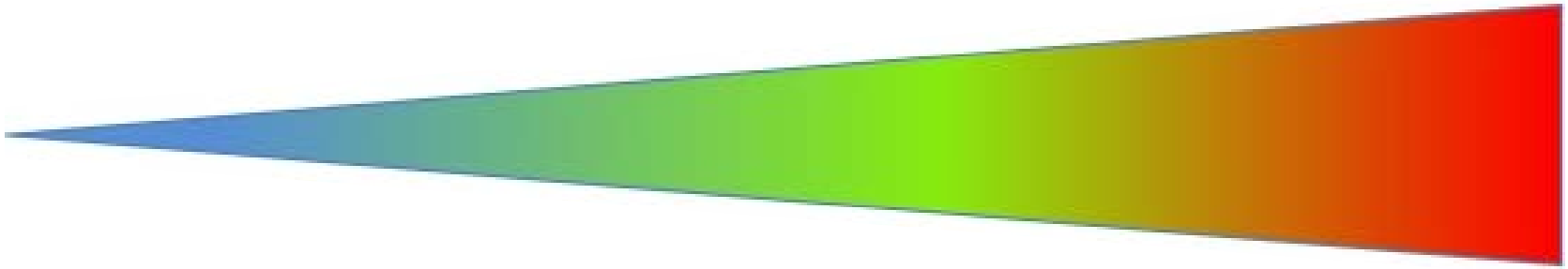
Normal leptin & adiponectin
- Appropriate energy stores

Appropriate response to antigen, normal cell survival, de-escalation after threat resolved

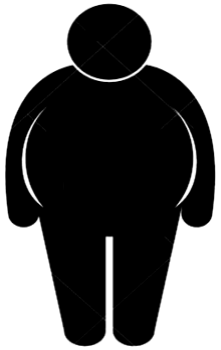


High leptin / low adiponectin
- Obesity

Lower barrier to cellular activation, high proliferation, robust cytokine production, impaired de-escalation



Conserved physiologic role



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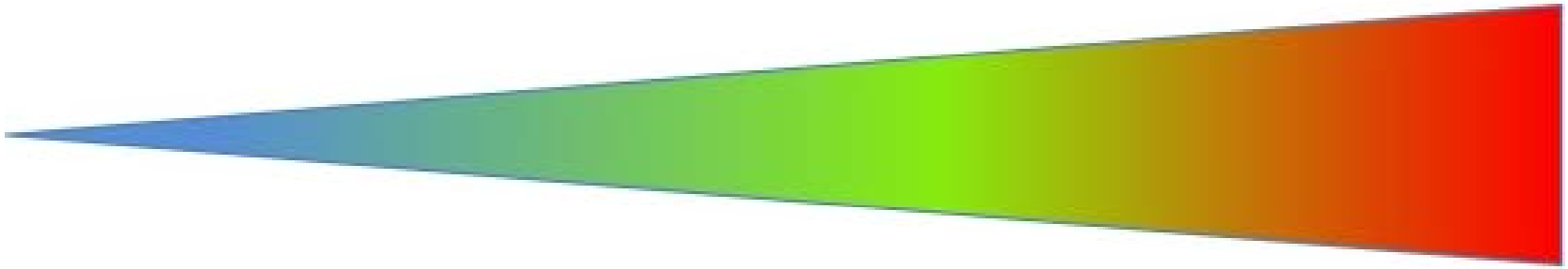

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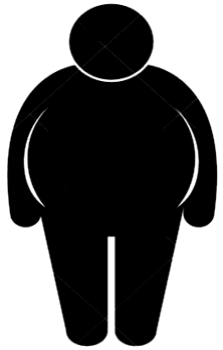
The World in 2018



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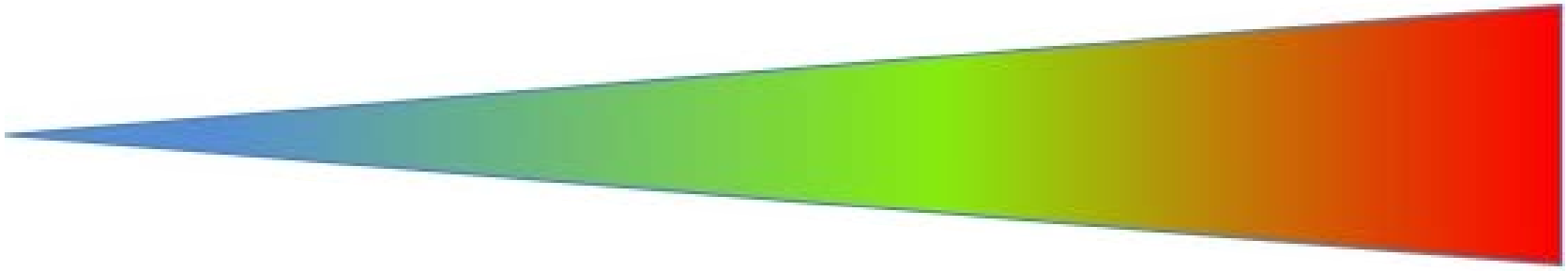

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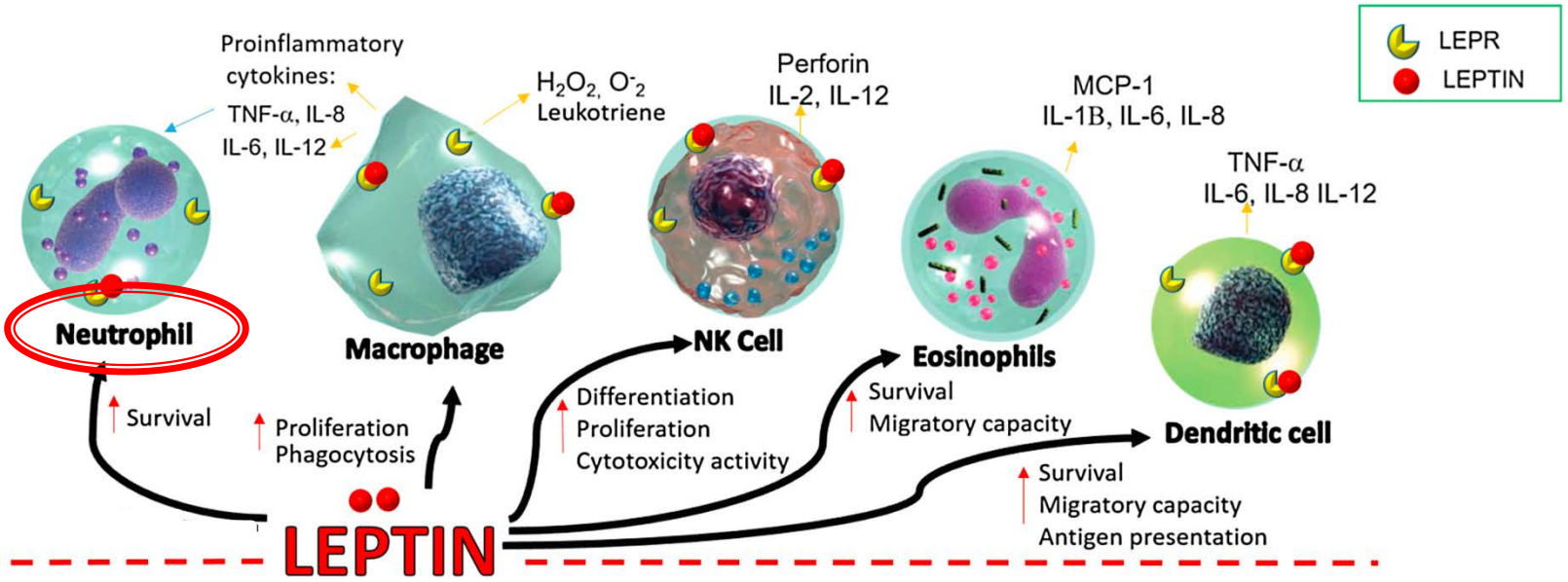
Highlights of leptin effects on innate immunity

Neutrophils:

- Reduced apoptosis
- Increased phagocytic activity
- Enhanced CD11b expression

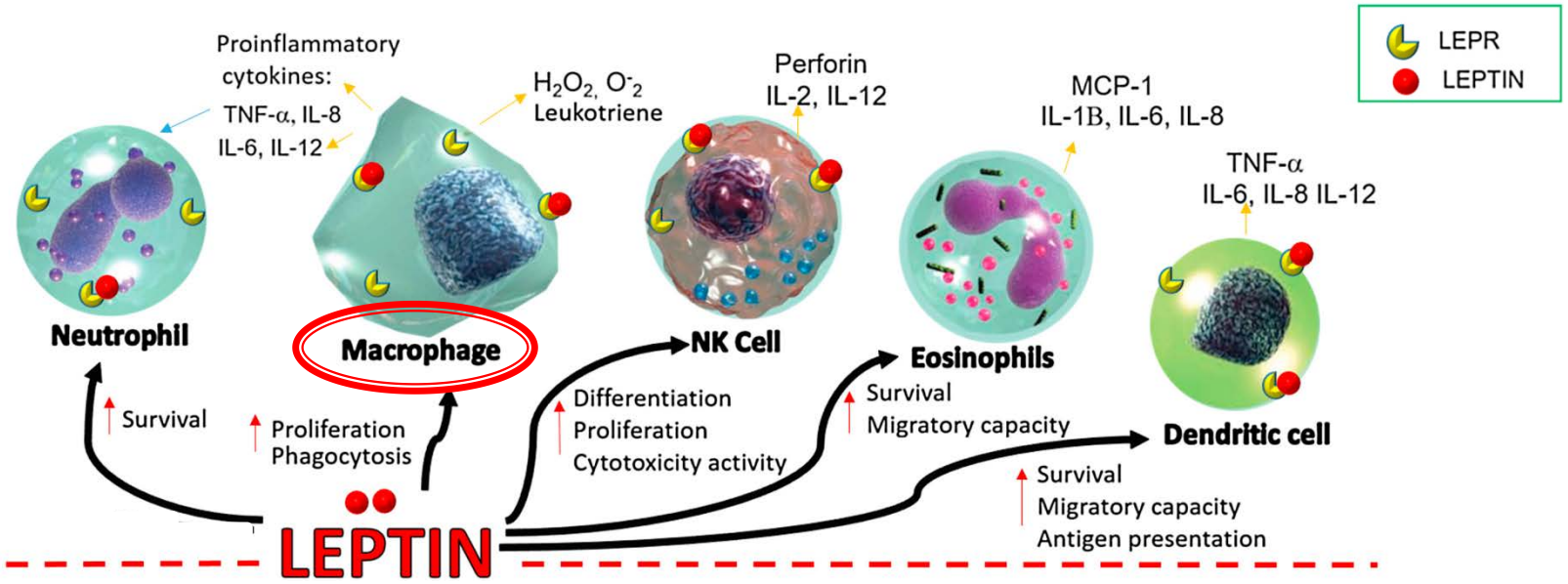


Perez-Perez A, *et al*. *Cytokine and Growth Factor Reviews*, 2017

Highlights of leptin effects on innate immunity

Monocytes/macrophages:

- Increased of phagocytic function
- Increased adhesion molecules
- Increased proliferation and activation marker expression (CD25, CD69)
- Increased TNF-α and IL-6 expression
- May serve as a chemoattractant in adipose tissue



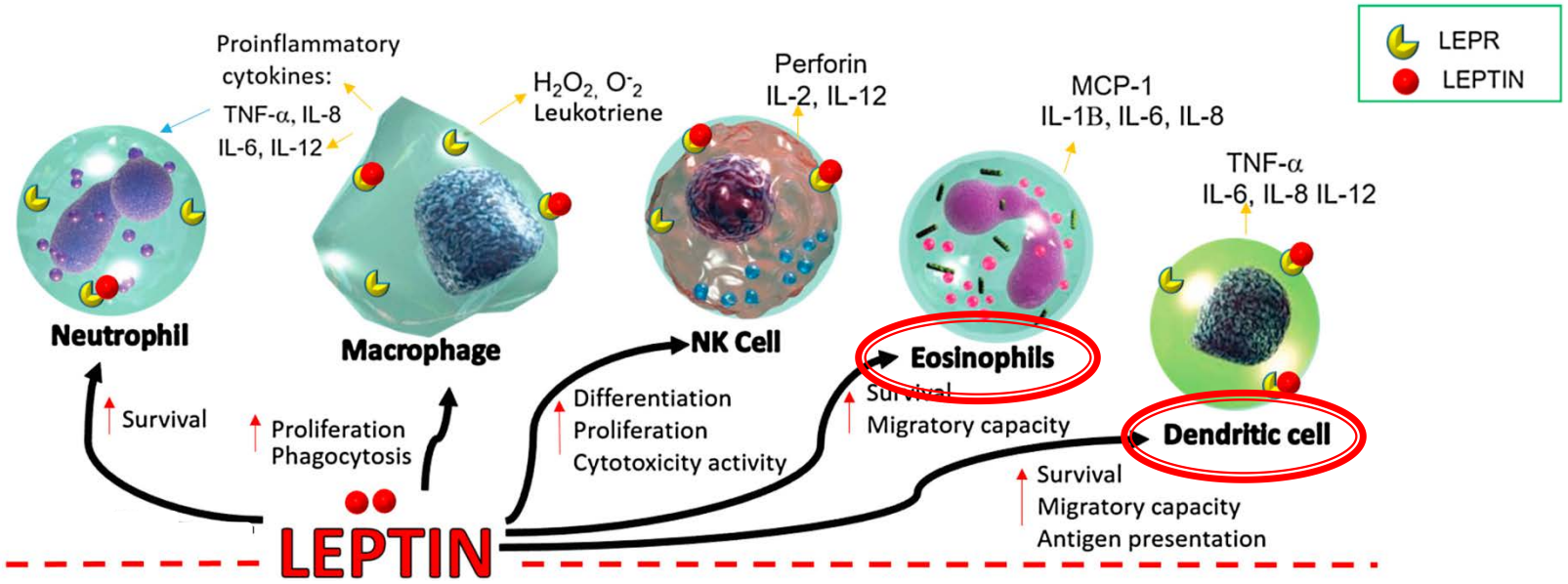
Highlights of leptin effects on innate immunity

Dendritic cells:

- Reduced apoptosis
- Shift towards T_H1 priming
- Increased TNF-α, IL-6, IL-8 production

Eosinophils:

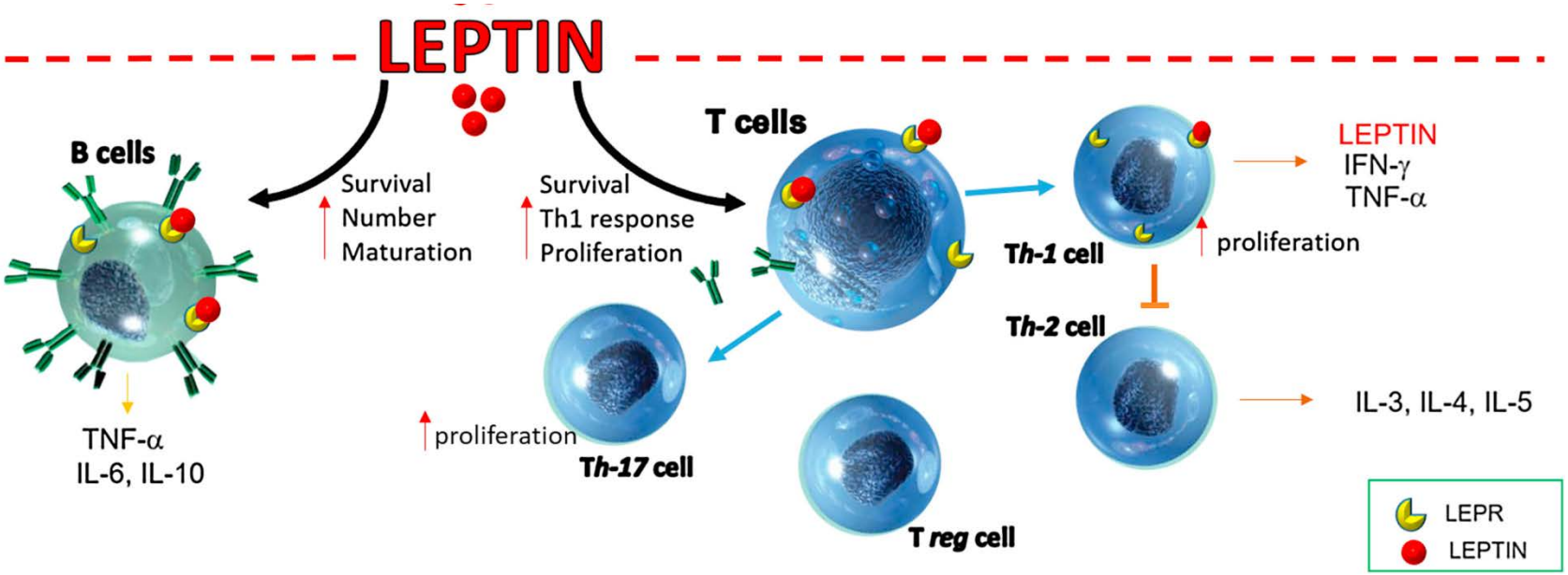
- Reduced apoptosis
- Increased activation
- Increased chemotaxis, migration, and adhesion molecule expression



Highlights of leptin effects on adaptive immunity

T cells:

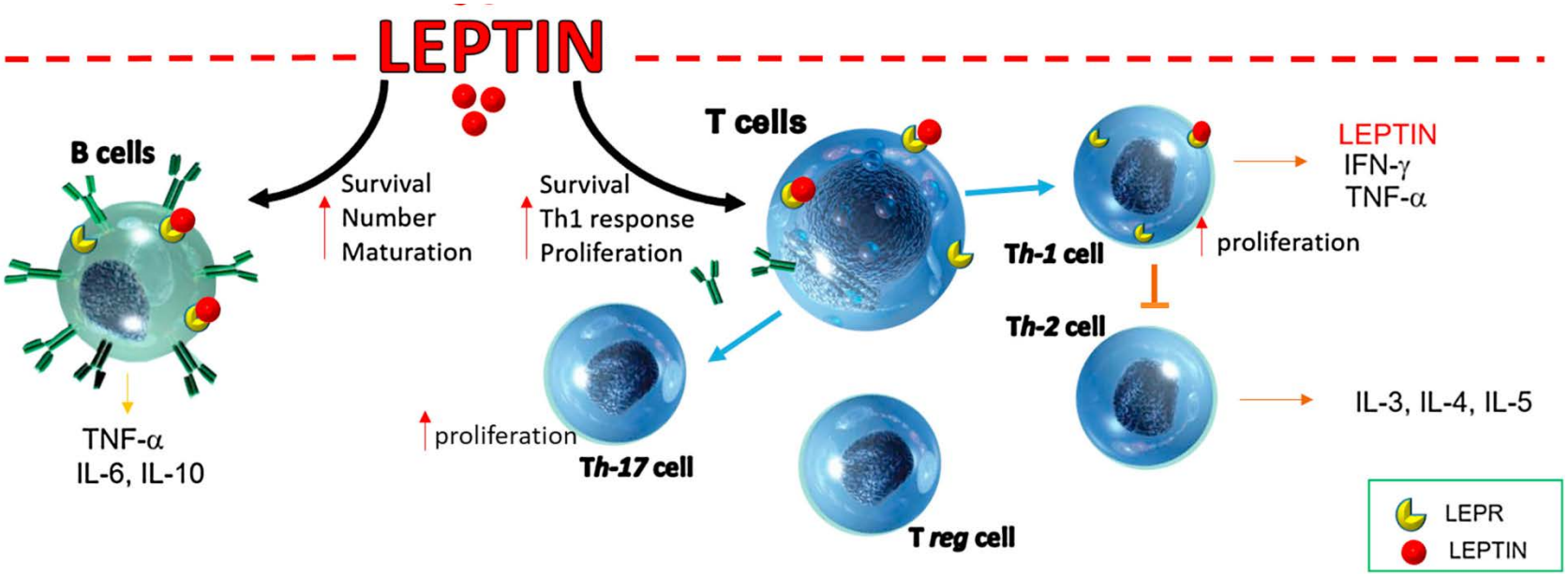
- Increases proliferation of naïve cells
- Activation of CD4+ T cells markedly increases leptin receptor expression (less on CD8+ T cells)
- Increases adhesion molecule expression and activation markers (CD69, CD25, CD71)



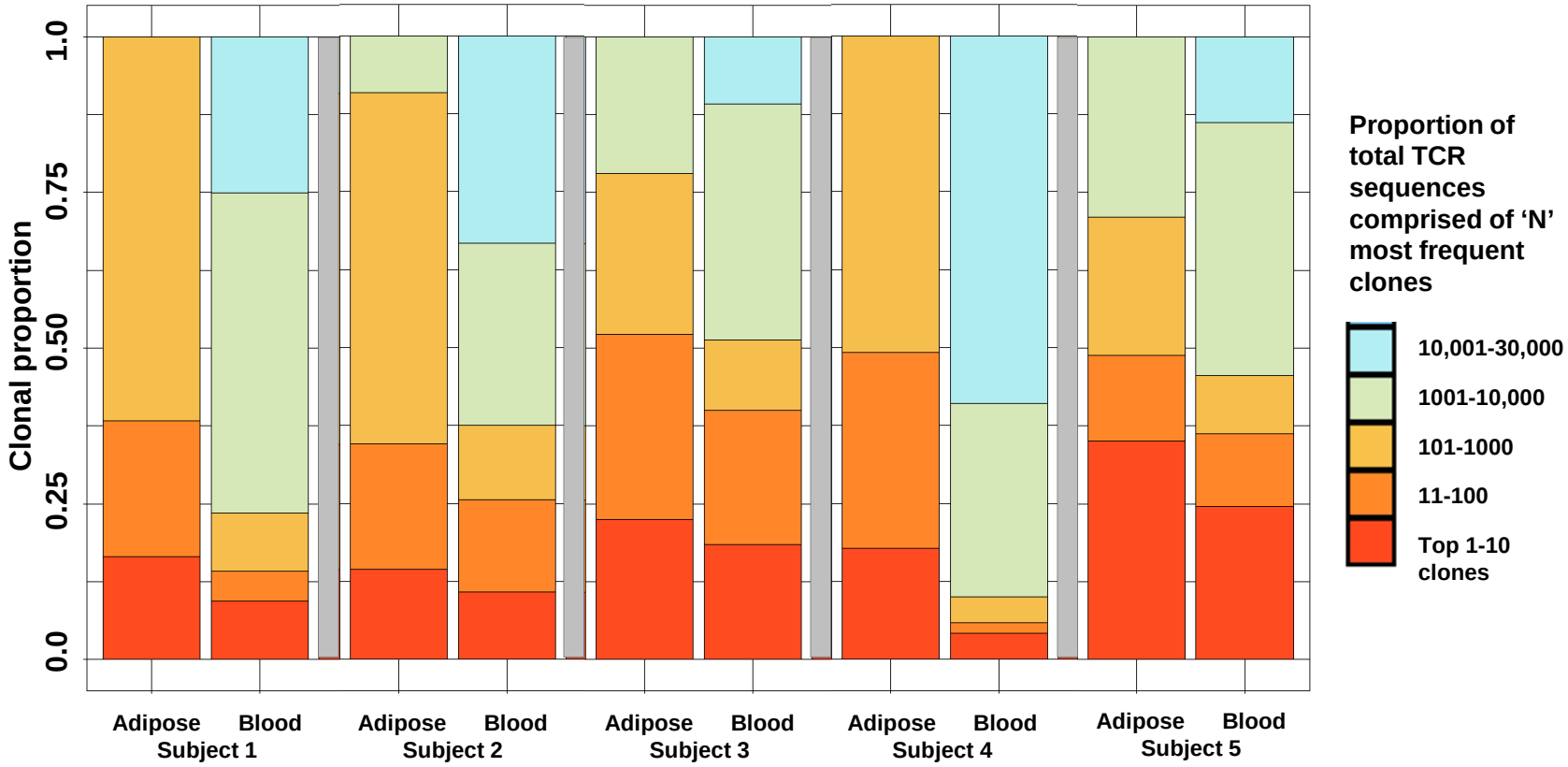
Highlights of leptin effects on adaptive immunity

T cells:

- Promotes expansion of activated CD4+ and CD8+ T cells
- Promotes polarization towards T_H1/T_H17 responses (sustained by autocrine loop of leptin section)
- Increased INF-ɣ, TNF-α expression
- Reduced Treg cell proliferation



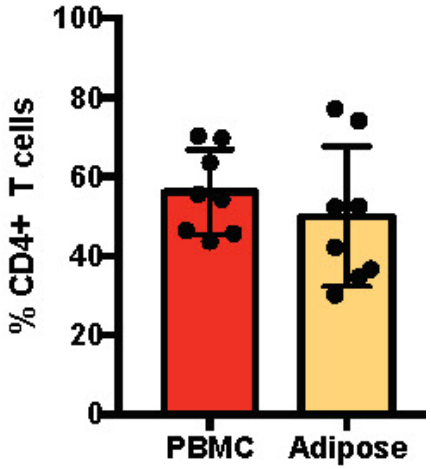
CD8+ T cells in adipose tissue are more clonal compared to blood in HIV+ persons

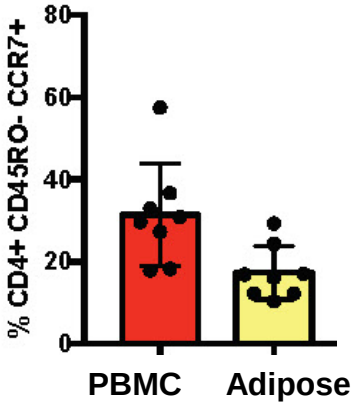


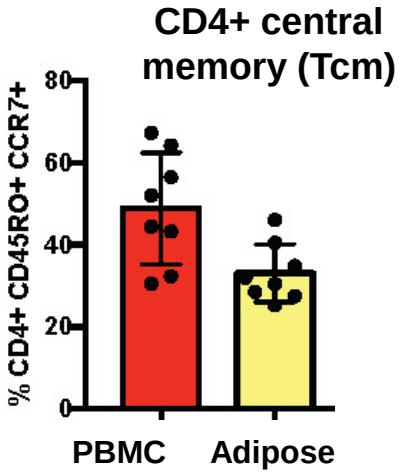
- **The 10 most prevalent T cell receptors comprise a larger percentage of the total repertoire in adipose tissue compared to paired blood (25% vs. 16%)**

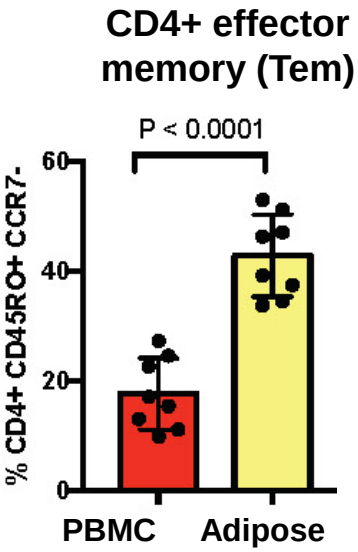
Koethe JR, *et al. JAIDS*. 2018

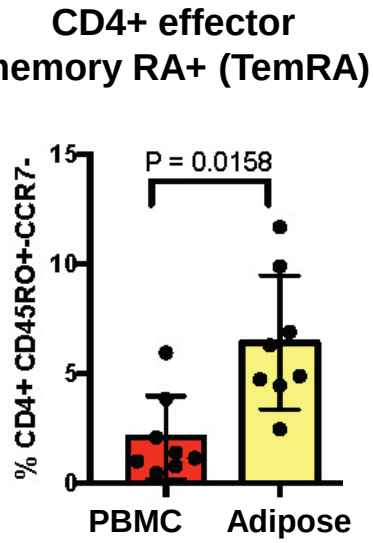
CD4+ T cell subsets in adipose tissue from HIV+ persons is enriched for effector memory cells











Wanjalla C, *unpublished*

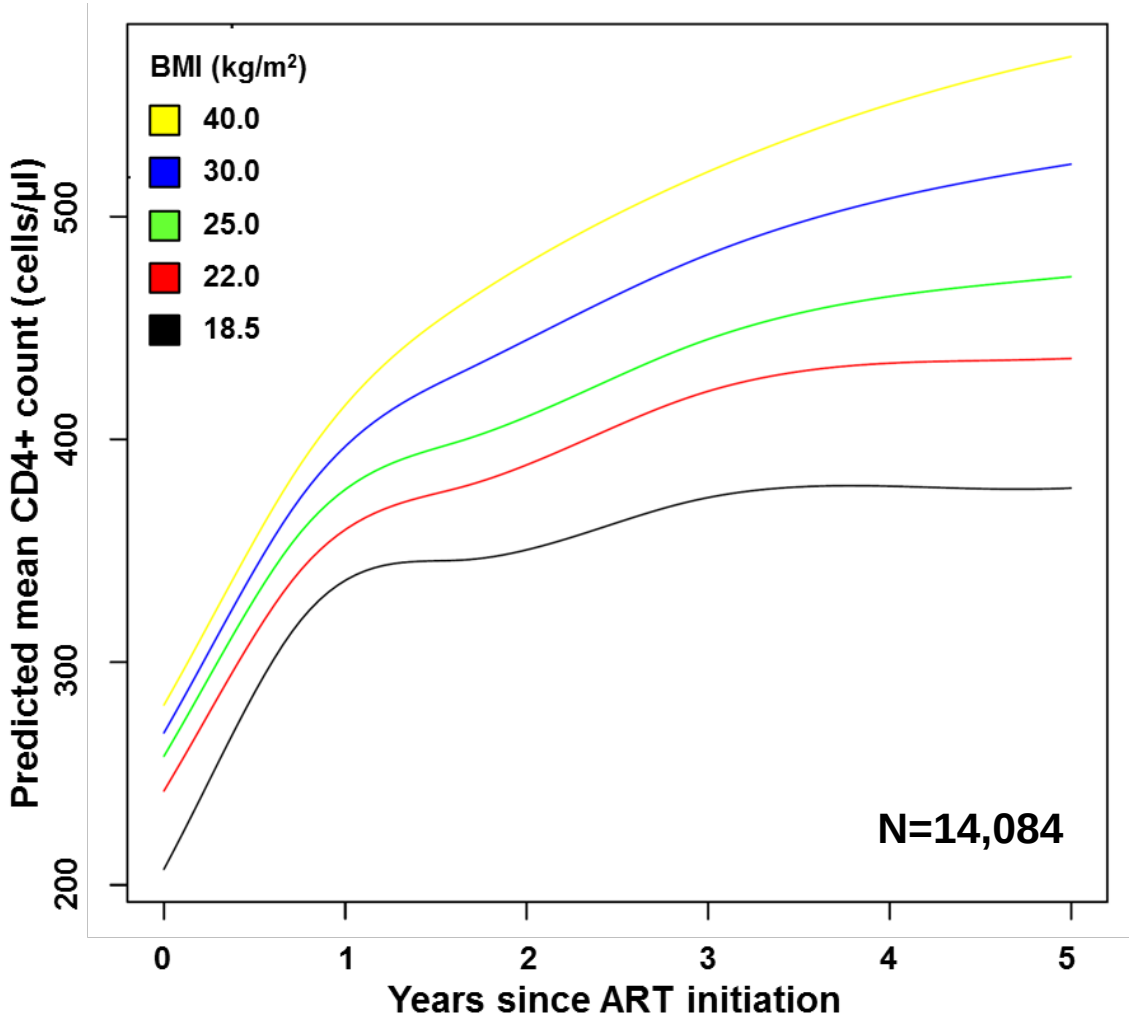
BMI and HIV progression in the pre-combination ART era

- A BMI $\geq$30 kg/m^2 was associated with a slower progression to a CD4 <200, AIDS-defining event or HIV-related death compared to a BMI 20-25 kg/m^2

- Each 1 kg/m^2 reduction in initial BMI was independently associated with a 24% increased risk of progression to AIDS over mean follow-up of 19 months

Shuter J *et al, JAIDS,* 2001; Jones C *et al, CID,* 2003.

Higher time-updated BMI accompanied by greater CD4+ T cell recovery on ART



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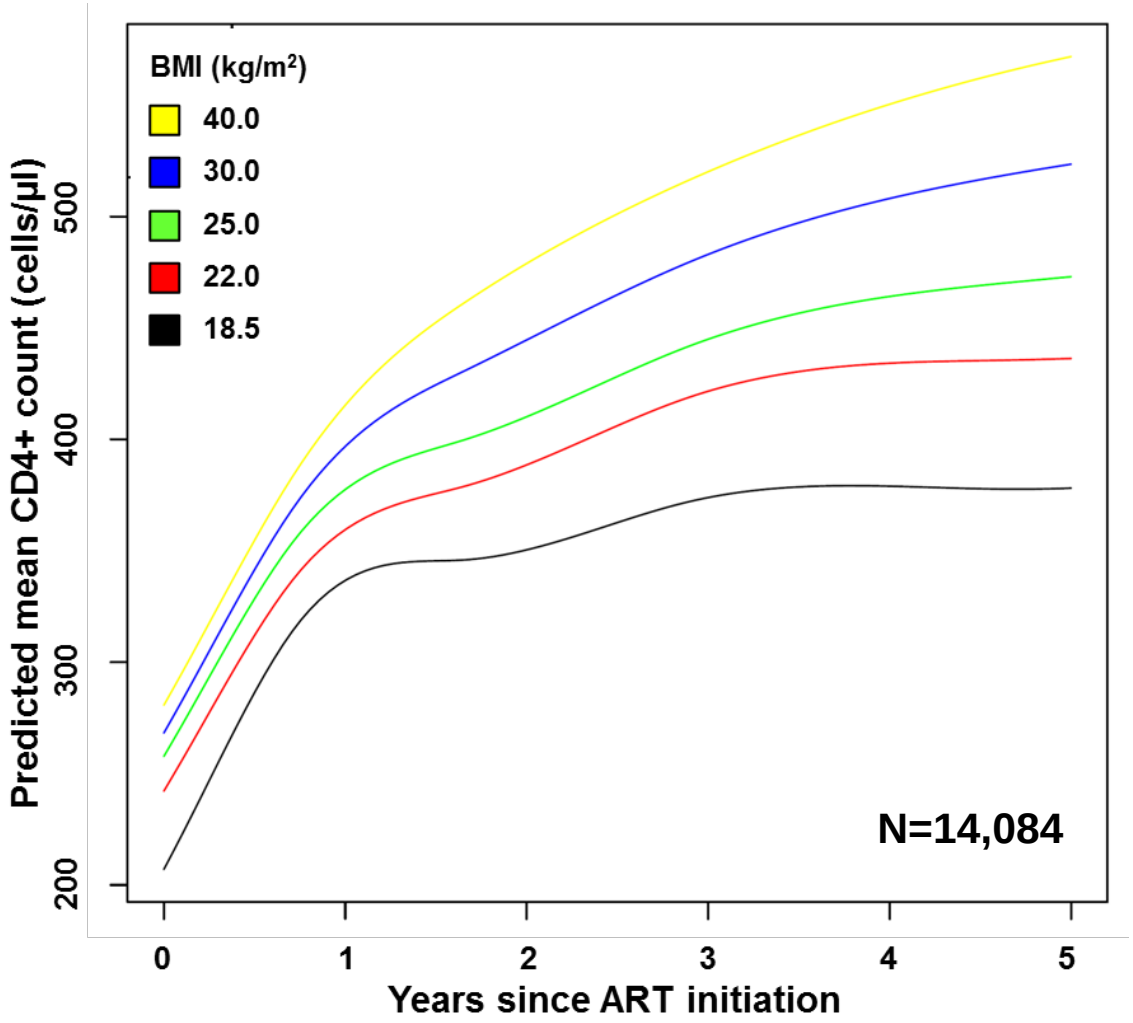
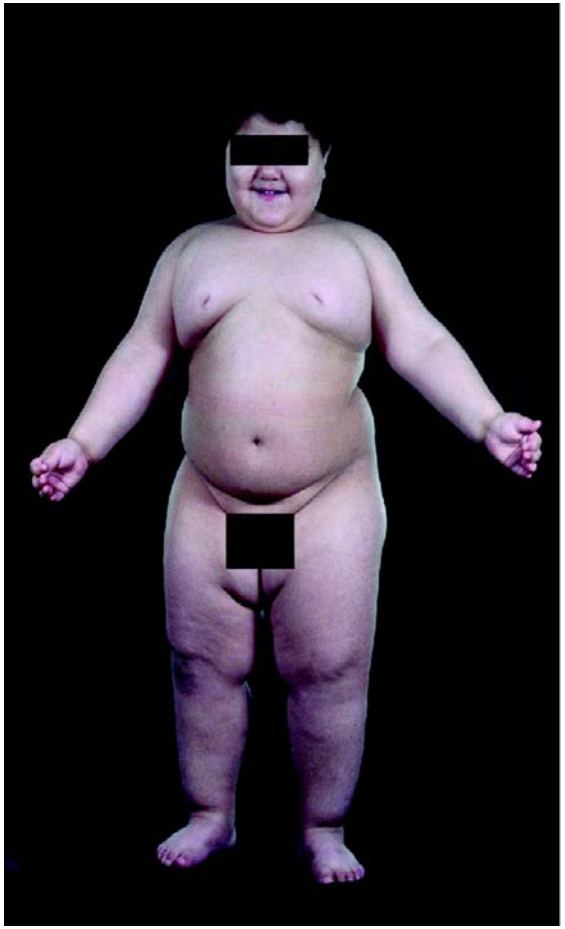


Could there be a role for leptin promoting immune recovery and/or response to opportunistic infections in HIV+ persons?

Koethe J, *et al. JAIDS.* 2016.

Recombinant leptin trials in HIV-negative children

- A 3-year-old boy with congenital leptin deficiency (*ob*$^{-}$/*ob*$^{-}$)
- Weight 42 kg before treatment with recombinant leptin
- Weight 32 kg after 4 years of treatment



Before leptin (age 3, 42 kg)

After leptin (age 7, 32 kg)

Farooqi IS & O'Rahilly S. *J Endocrinol* 2014;
Farooqi IS, *et al. JCI.* 2002.

Recombinant leptin trials in HIV-negative children

Proliferative responses of PBMCs to T-cell stimuli before and after leptin treatment

Cell type	-6 months	Treatment start	+2 months	+6 months	+10 months	Normal range (child age 3; cells/mm^3)
CD3$^+$ (%)	2,686 (49%)	2,416 (58)	1,893 (51)	3,262 (72)	3,087 (66)	1,200-2,500 (65-82%)
CD4$^+$ (%)	750 (18%)	866 (21)	927 (24)	1,468 (31)	1,358 (29)	1,000-2,000 (30-50%)
CD8$^+$ (%)	1,836 (26%)	1.450 (25)	850 (22)	1,468 (31)	1,543 (33)	240-1,000 (25-35%)
CD19$^+$ (%)	2,189 (31%)	1,525 (37)	1,468 (38)	1,247 (26)	1,216 (26)	200-400 (8-15%)

Farooqi IS, *et al. JCI.* 2002.

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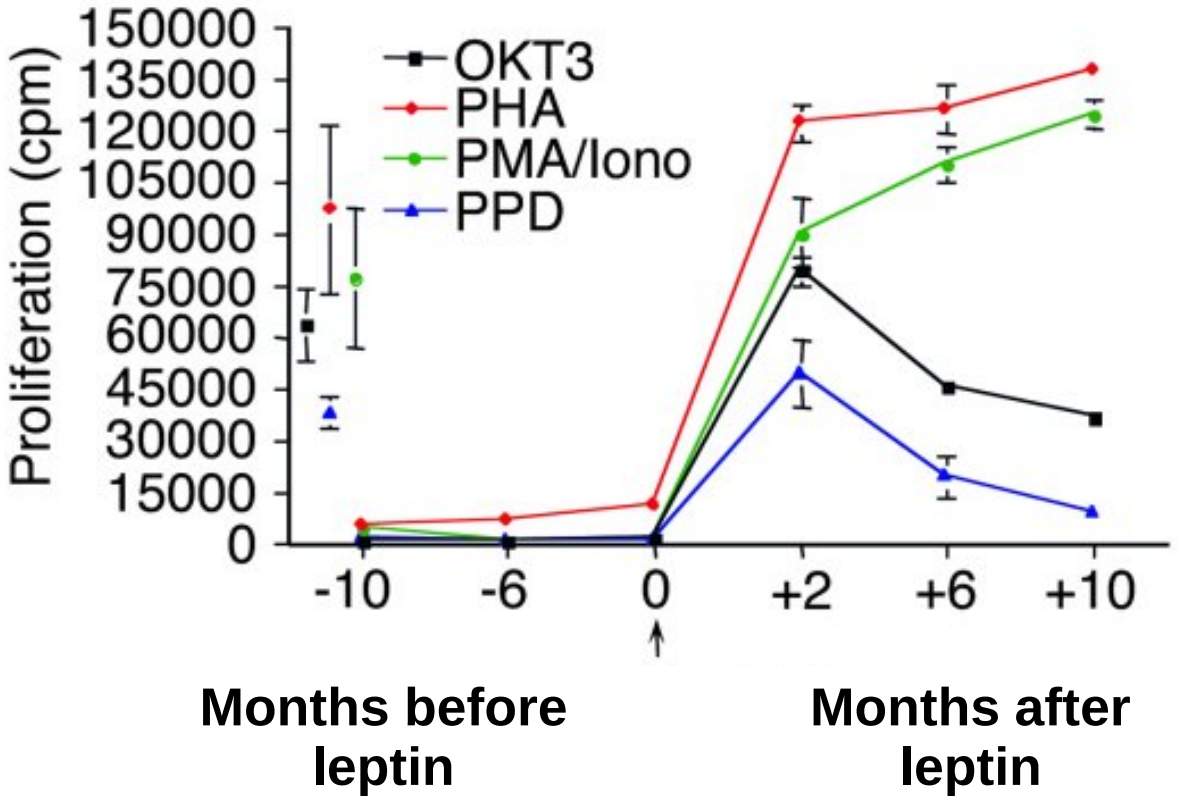

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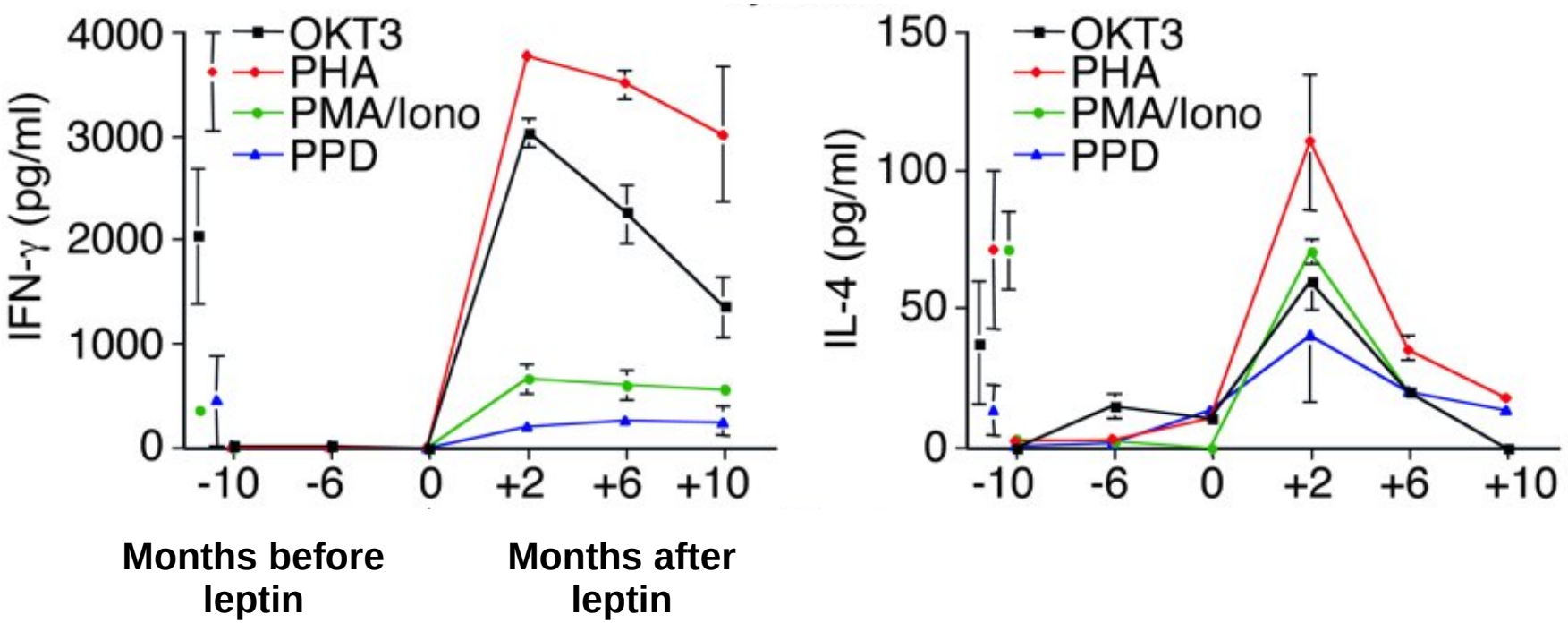
Recombinant leptin trials in HIV-negative children

Cytokine responses of PBMCs to T-cell stimuli before and after leptin treatment



Farooqi IS, *et al. JCI.* 2002.

Recombinant leptin trials in HIV-associated lipodystrophy - summary

Study (year)	Design	Subjects & Duration	Change in leptin levels (ng/ml)	Beneficial effect on			Adverse effects
				Glucose metabolism	Lipid metabolism	Steatohepatitis	
Lee *et al.* (2006)	Randomized crossover	7 M (LD-HIV) 4 months	1.34 to NR	+	+	–	None major
Mulligan *et al*. (2009)	Prospective open-label	8 M (LD-HIV) 6 months	2.7–21.3	+	++	NR	None Major
Magkos *et al*. (2011)	Double blind placebo controlled	9 M (LD-HIV) 3 months	3.7–16.5	+	–	+	Injection site reaction (1)
Sekhar *et al*. (2012)	Double-blind placebo controlled	17 M (LD-HIV) 4 months	2.6–34.4	+	improved non-HDL-C, no change in lipid kinetics	NR	Weight loss (2), decline in $CD4^+$ T-cell count (1)

No significant improvements in CD4+ T cell count in these studies

Simha V. *Expert Rev Endo and Metab.* 2014.

Potential future research areas

•Use of recombinant leptin to boost CD4 recovery or response to opportunistic infections among in malnourished (e.g., BMI <18.5 kg/m2) persons in resource-limited settings.

•HIV+ persons have a high adipose CD8+ cells and low CD4+, as seen in obesity, but less macrophage activation and CD4+ subset changes. Are lower tissue leptin levels a factor in this disparity between HIV and obesity?

•Will there be a potential role for *AdipRon* (new, oral adiponectin-receptor agonist) in persons with HIV – either for improving insulin sensitivity or reducing immune activation?

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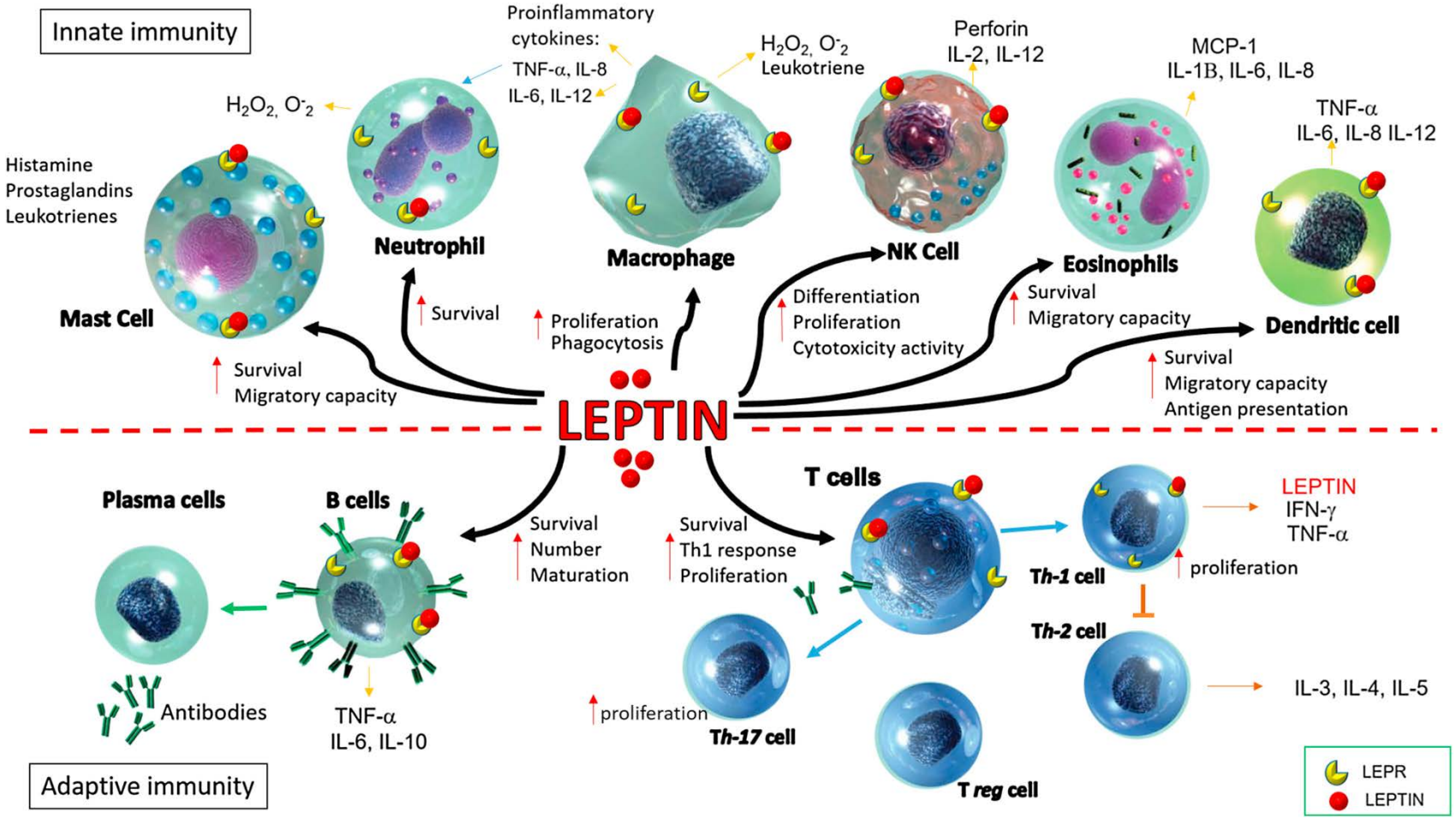
VANDERBILT UNIVERSITY MEDICAL CENTER

TN CFAR TENNESSEE CENTER FOR AIDS RESEARCH


Innate immunity
Proinflammatory cytokines:
TNF-α, IL-8
IL-6, IL-12
H_2O_2, O^-_2
H_2O_2, O^-_2
Leukotriene
Perforin
IL-2, IL-12
MCP-1
IL-1B, IL-6, IL-8
TNF-α
IL-6, IL-8 IL-12
Histamine
Prostaglandins
Leukotrienes
Neutrophil
Macrophage
NK Cell
Eosinophils
Dendritic cell
Mast Cell
Survival
Proliferation
Phagocytosis
Differentiation
Proliferation
Cytotoxicity activity
Survival
Migratory capacity
Survival
Migratory capacity
Survival
Migratory capacity
Antigen presentation
LEPTIN
Plasma cells
B cells
T cells
Survival
Number
Maturation
Survival
Th1 response
Proliferation
LEPTIN
IFN-γ
TNF-α
Th-1 cell
proliferation
Th-2 cell
IL-3, IL-4, IL-5
Antibodies
TNF-α
IL-6, IL-10
proliferation
Th-17 cell
T reg cell
LEPR
LEPTIN
Adaptive immunity

Outline

- Pleiotropic effects of adipokines
- Adipokines and immune function
- Recombinant human leptin in HIV+ and HIV-negative person
- Research gaps and possible future studies

Adipokines and hsCRP in HIV+ persons

- Cross-sectional study of 106 HIV+ adults on >24 weeks of ART
- BMI range from <20 to >35 kg/m^2

Relationship of serum adipokine levels and hsCRP level		
	β (95% CI)	**Adjusted P value**
Leptin	1.95 (1.36, 2.80)	<0.001
Adiponectin	0.74 (0.45, 1.21)	0.23
Resistin	1.27 (0.90, 1.80)	0.18

Models adjusted for age, sex, CD4+ lymphocyte count (in 100 cell/uL strata), smoking status, and non-steroidal anti-inflammatory drug, aspirin, and protease inhibitor use.

Koethe J *et al, ARHR,* 2012

Adipokines and hsCRP in HIV+ persons

Effect of body composition on hsCRP with and without adjustment for leptin

Body composition variable	Without adjustment for leptin		With adjustment for leptin	
	β1	P value	β2	P value
Body mass index	1.57	0.02	1.22	0.54
Waist-to-hip ratio	1.58	<0.01	1.22	0.03
Limb fat	1.82	0.05	1.10	0.85
Total body fat	2.16	<0.01	1.41	0.50
Total body % fat	2.45	<0.01	1.62	0.31
Trunk fat	2.55	<0.01	1.83	0.21
Trunk % fat	2.88	<0.01	2.04	0.12

Leptin mediated the relationship of BMI and DEXA absolute limb fat, body fat, and trunk fat with circulating hsCRP

Koethe J *et al, ARHR,* 2012