

## Neuroimmunity in Obesity and Cardiac function

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### Project outline

#### Background

Adipose tissue is controlled by peripheral neural circuits that are necessary and sufficient for *localized* fat mass reduction (Cell 2015, Nature Comm 2017). Specifically, we discovered that the neuro-adipose junction drives lipolysis via *local* norepinephrine (NE) release. Moreover, we discovered Sympathetic neuron-Associated Macrophages (SAMs; Figure 1) that directly regulate the extracellular availability of norepinephrine (NE) and that, upon obesity onset, are excessively recruited to sympathetic nerves in adipose depots. SAMs are not, however, recruited to the SNS innervation of other organs during obesity. Genetic abrogation of the mechanism for the uptake of NE by SAMs increases NE availability, which in turn promotes thermogenesis and browning, as well as long-term amelioration of obesity independently of food intake (Nature Med 2017). As SAMs also exist in humans, this molecular mechanism could be therapeutically exploited provided that we identify a constellation of tissue-specific markers/cells within the neuroimmune niche in adipose tissues.

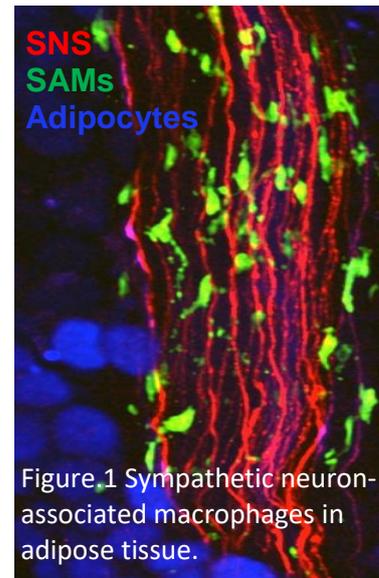


Figure 1 Sympathetic neuron-associated macrophages in adipose tissue.

#### Hypothesis

Our preliminary data demonstrate that the neuroimmune niche that controls SAMs consists of heterogeneous populations of cells. We hypothesize that **a specialized population of immune cells (CD45+) residing in the sympathetic neuro-adipose junctions become molecularly altered upon obesity to facilitate the recruitment of SAMs to adipose tissues.** Given that SAMs are not recruited to the SNS innervation of other organs during obesity, we propose that the molecular signatures of these resident cells are organ-specific, and thus constitute a suitable druggable cellular target that will drive a *local* sympathomimetic response within adipose depots avoiding cardiac complications associated with sympathetic upregulation.

## Goals

Our goal is to characterize the cellular players in the sympathetic neuroimmune niche in adipose depots, as well as in the cardiac sympathetic stellate ganglia by single cell sequencing. This molecular /cellular analysis will be first made in rodent models, and will be subject to subsequent validation in human SNS tissues<sup>1,5</sup>. The generated cellular footprint will open new avenues of research for follow up human validation of the identified key immune cell populations and, in the future, will guide the development to new pharmacotherapies for obesity, as well as associated cardiac dysfunction.

## Aims

1. Characterize the SNS-resident leucocytes in adipose SNS nerves by single cell sequencing and compare lean versus obese mouse models.
2. Characterize the SNS-resident leucocytes in stellate ganglia (which innervate the heart), such as to differentially screen the cellular and molecular candidates identified in Aim 1
3. Compare RNA-seq of SNS-resident leucocytes in stellate ganglia with existent RNAseq data of normotensive and hypertensive mouse models and humans<sup>1,5</sup>.

## Contributions

Fang Zhang will contribute with the single cell sequencing at Novo Nordisk; Domingos lab will provide the samples and contribute on global oversight of testing any hypothesis originating from the big data set (follow up validation by FACS, rt PCR, conditional KO, metabolic phenotyping, etc); Udalova lab will contribute with expertise in bioinformatics and molecular characterisation of immune cells; Paterson lab will contribute with in vitro validation pertaining to cardiac and sympathetic neurophysiology, and share RNAseq data of normotensive and hypertensive rat models and humans<sup>5</sup>.

## Supervisor's recent relevant publications

1. Pirzgalska RM, Seixas E, Seidman JS, Link VM, Martínez Sánchez N, Mahú I, Mendes R, Gres V, Kubasova N, Morris I, Arús BA, Larabee CM, Vasques M, Tortosa F, Sousa AL, Anandan S, Tranfield E, Hahn MK, Iannacone M, Spann NJ, Glass CK, **Domingos AI**. [Sympathetic neuron-associated macrophages contribute to obesity by importing and metabolizing norepinephrine](#). *Nature Medicine*. 2017; 23:1309-1318.
2. Pereira MMA, Mahú I, Seixas E, Martínéz-Sánchez N, Kubasova N, Pirzgalska RM, Cohen P, Dietrich MO, López M, Bernardes GJL, **Domingos, AI**. [A brain-sparing diphtheria toxin for chemical genetic ablation of peripheral cell lineages](#). *Nature Communication*. 2017 3; 8:14967.
3. Zeng W, Pirzgalska RM; Pereira MMA; Kubasova N; Barateiro A; Seixas E; Lu YH; Kozlova A; Voss H; Martins GG; Friedman JM, **Domingos AI**. [Sympathetic Neuro-Adipose Connections Mediate Leptin-Driven Lipolysis](#). *Cell*. 2015 24; 163:84-94.
4. Dalmas E, Toubal A, Alzaid F, Blazek K, Eames HL, Lebozec K, Pini M, Hainault I, Montastier E, Denis RGP, Ancel P, Lacombe A, Ling Y, Allatif O, Cruciani-Guglielmacci C, André S, Viguier N, Poitou C, Stich V, Torcivia A, Foufelle F, Luquet S, Aron-Wisnewsky J, Langin D, Clément K, **Udalova IA**, Ventecléf N. [Irf5-deficiency in macrophages promotes beneficial adipose tissue expansion and insulin sensitivity during obesity](#). *Nature Medicine*. 2015 21:610-8.
5. Bardsley EN, Davis H, Ajjjola OA, Buckler KJ, Ardell JL, Shivkumar K, **Paterson DJ**. [RNA Sequencing Reveals Novel Transcripts from Sympathetic Stellate Ganglia During Cardiac Sympathetic Hyperactivity](#). *Scientific Reports*. 2018 8:8633.