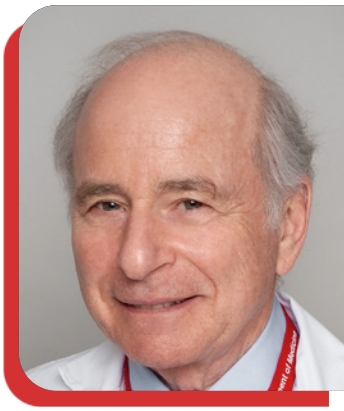
PERSPECTIVES IN HYPERTENSION

Immunological insights into hypertension



ERNESTO SCHIFFRIN

Director, Hypertension and Vascular Research Unit,
Lady Davis Institute for Medical Research, Montreal, Canada

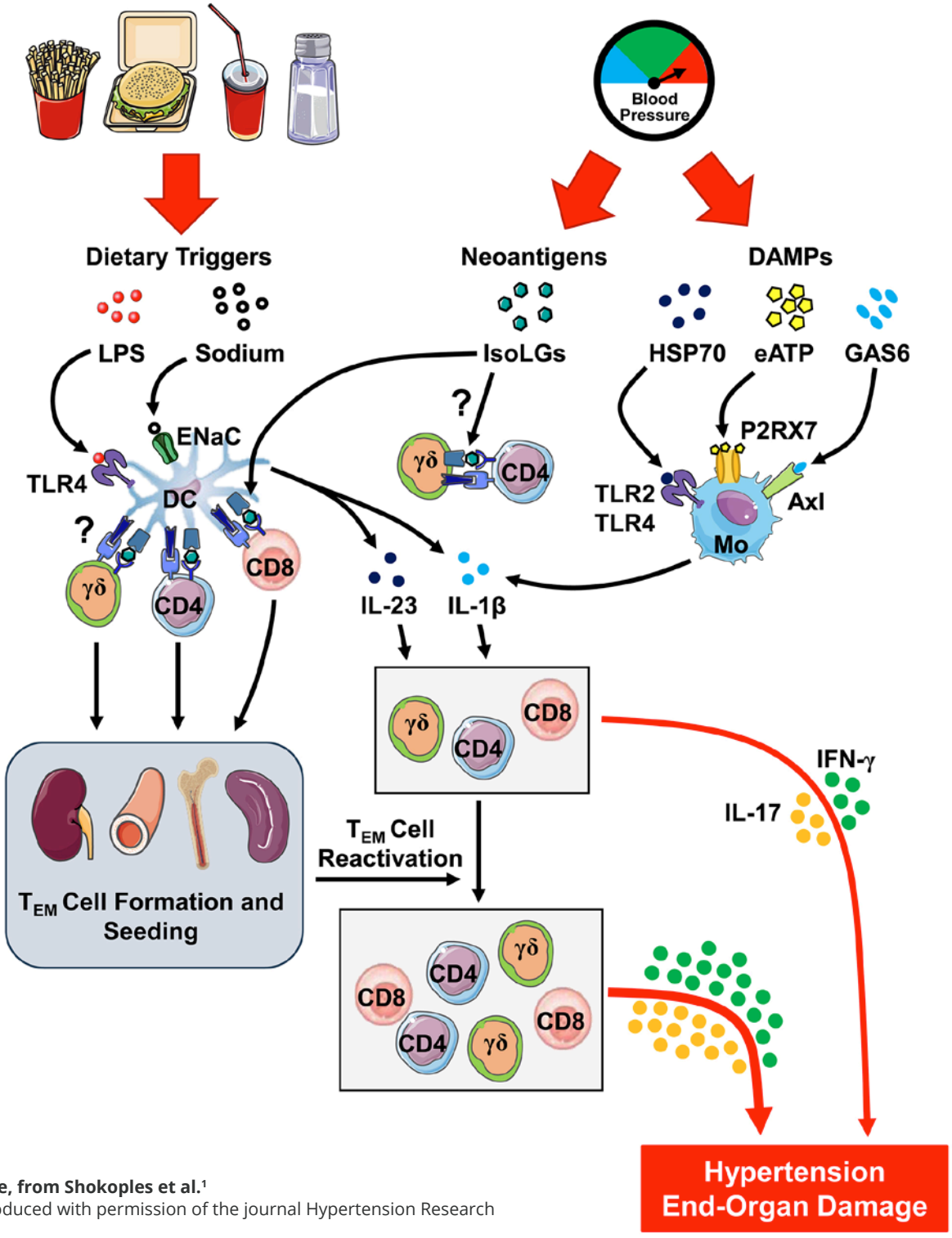
The first author of the paper "Immunological insights into hypertension: unraveling triggers and potential therapeutic avenues",[1] was Brandon Shokoples. Brandon recently obtained his PhD at McGill University working in my lab, and is now an MD student in Calgary, AB, Canada. The manuscript was commissioned as part of the Japanese Society of Hypertension (JSH) 14th Hypertension Research Award, which was awarded for the paper Shokoples B. et al Hypertension Res. 2023; 46(1):40-49.[2]

Hypertension remains the leading cause of morbidity and mortality worldwide. Despite its prevalence, the development of novel antihypertensive therapies has only recently picked up, with a number of novel agents which are not yet available commercially. This, despite the fact that a substantial proportion of individuals do not respond or are non-adherent to existing treatments.

In this paper,[1] we reviewed some of the history of the immune hypothesis of hypertension and its mechanisms, as well as the potential for novel immune treatments of the "silent killer". Although several investigators noted the presence of abundant immune cells around blood vessels in different target tissues in experimental hypertension, it was not until 2002-2005 that we identified for the first time the involvement of the innate immune system and specific immune cells, macrophages/monocytes, in angiotensin II-induced hypertension,[3,4] and 2007, that David Harrison's group showed the role of adaptive immunity and T cells in similar models of hypertension.[5]

Since then, an increasingly abundant literature has demonstrated that chronic low-grade inflammation participates to an important degree in the triggering and sustained elevation of blood pressure in both experimental animals and in humans.[6] Salt and pathogen-associated as well as damage-associated molecular patterns (PAMPs and DAMPs) play roles in activating the immune system. Diets rich in fat or sodium promote inflammation by favoring passage of toxins and bacteria through the intestinal barrier and by triggering salt-sensitive receptors in dendritic cells and T cells. DAMPs, such as extracellular adenosine triphosphate and heat-shock protein (HSP) 70 released secondary to tissue injury during episodes of increased blood pressure, contribute to immune cell activation and inflammation. We have shown how unconventional lymphocytes such as the innate-like γδ T cells participate in the initiation and maintenance of an immune response through involvement in experimental and human hypertension in antigen presentation and regulating cytokine-mediated responses.[7,8] Immunological memory resulting from generation of effector memory T cells after exposure to hypertensive insults maintains the immune response in hypertension.[9] These memory cells can be activated, and then participate in the mechanisms of elevated blood pressure and target organ damage. Recent evidence from human hypertension agrees with distinct immune pathways in human hypertension,[10] creating an opportunity for targeted immune interventions. Reduction in anti-inflammatory T regulatory lymphocytes (Treg) may favor the persistent state of low grade inflammation.[11-14] Small elevations of blood pressure induced by salt in susceptible individuals lead to

microbiome-dependent intestinal wall immune cell activation and through microbiome-derived short chain fatty acids to hemodynamic changes and endothelial and kidney damage, generation of neoantigens and DAMPs, and together with other insults such as lipopolysaccharides (LPS), sodium, heat-shock protein (HSP)70, extracellular adenosine triphosphate (ATP), and growth arrest-specific 6 (GAS6), activate the innate immune system, including dendritic cells (DCs) and monocytes through their respective receptors (toll-like receptor [TLR]4, amiloride-sensitive epithelial sodium channel, TLR2/4, P2X7 receptor [P2RX7],[15] and Axl). This leads to costimulatory



Figure, from Shokoples et al.[1]
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molecule expression and interleukin (IL)-1β and IL-23 production.[2] The neoantigens HSP70 and isolevuglandins[16] generated within antigen presenting cells activate T effector cells by DCs and possibly γδ T cells, resulting in production of cytokines IL-17[17] and interferon (IFN)-γ,[2] and formation of T effector memory (T_{EM}) cells in the kidney, perivascular adipose tissue, bone marrow, and spleen. Exposure of T_{EM} cells to their cognate antigen or previous activating stimuli causes these cells' rapid expansion and activation. This inflammatory condition thus contributes to blood pressure elevation and target organ injury. The process of activation of the immune system and target organ damage is depicted in the figure. Target organ injury feeds back into immune activation leading to further tissue injury and blood pressure elevation.

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Ernesto Schiffrin – ernesto.schiffrin@McGill.Ca