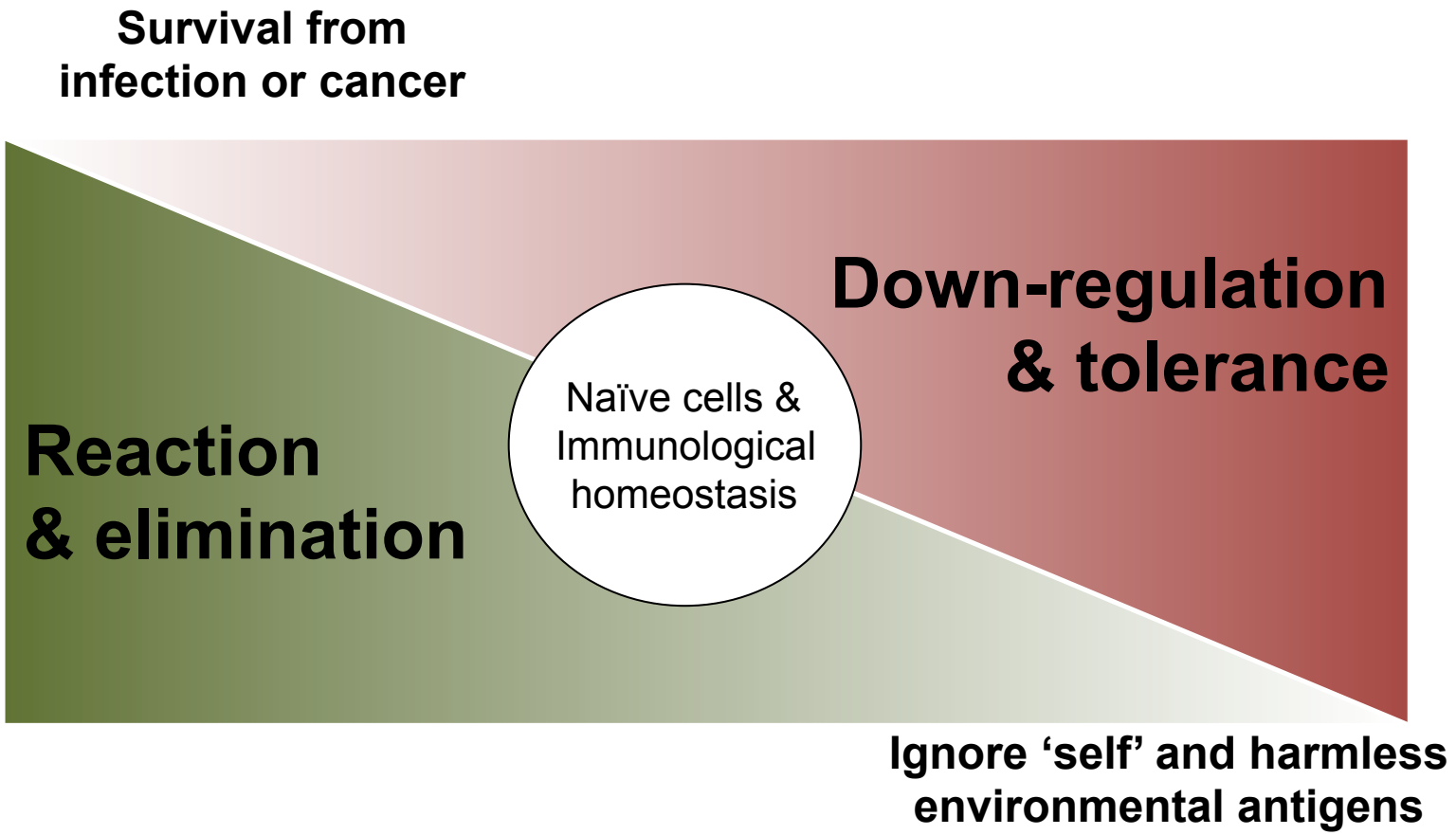
Environmental Exposures and Immune Function

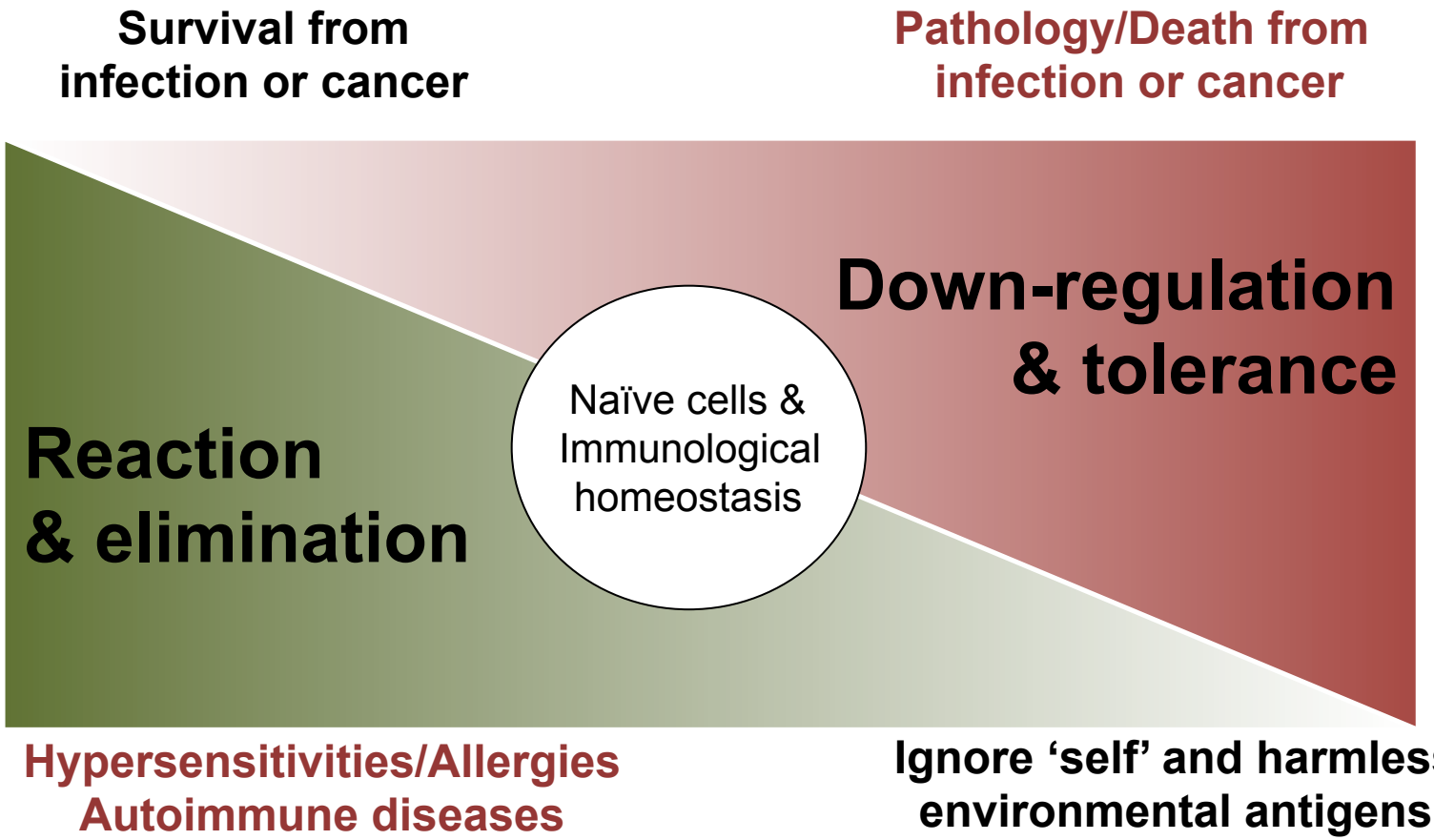
Presented by Dr. B Paige Lawrence
Professor of Environmental Medicine and of Microbiology & Immunology
University of Rochester School of Medicine and Dentistry

Images: leadminorityreport.net;cytokines_nordicbiosite.dk;brighamandwomens.org; bpabottles.cbc.ca; cleanandhealthyme.org; sciencedaily.org; genderandhealth.ca

Immunoregulatory balance is key to maintaining health and preventing disease



Immunoregulatory balance is key to maintaining health and preventing disease



Many factors are known to influence the function of the immune system

- Age
- Sex (including endocrine status)
- Genetics (and epigenetics)
- Physical fitness
- Nutritional and psychological status
- Existing biota (infection, normal microflora)
- Physical environment (seasonal changes, geographical location)
- Exposures to exogenous chemicals (good or bad)

Immunotoxicology/Immunopharmacology encompass three important areas

Academic research

What is the mechanism?

Can we develop or refine new therapies by understanding toxicity?

Can we improve public health by defining causality?

Industry research

How can we modulate or use the immune system to treat disease?

Will a new drug have unexpected and detrimental effects on the immune system?

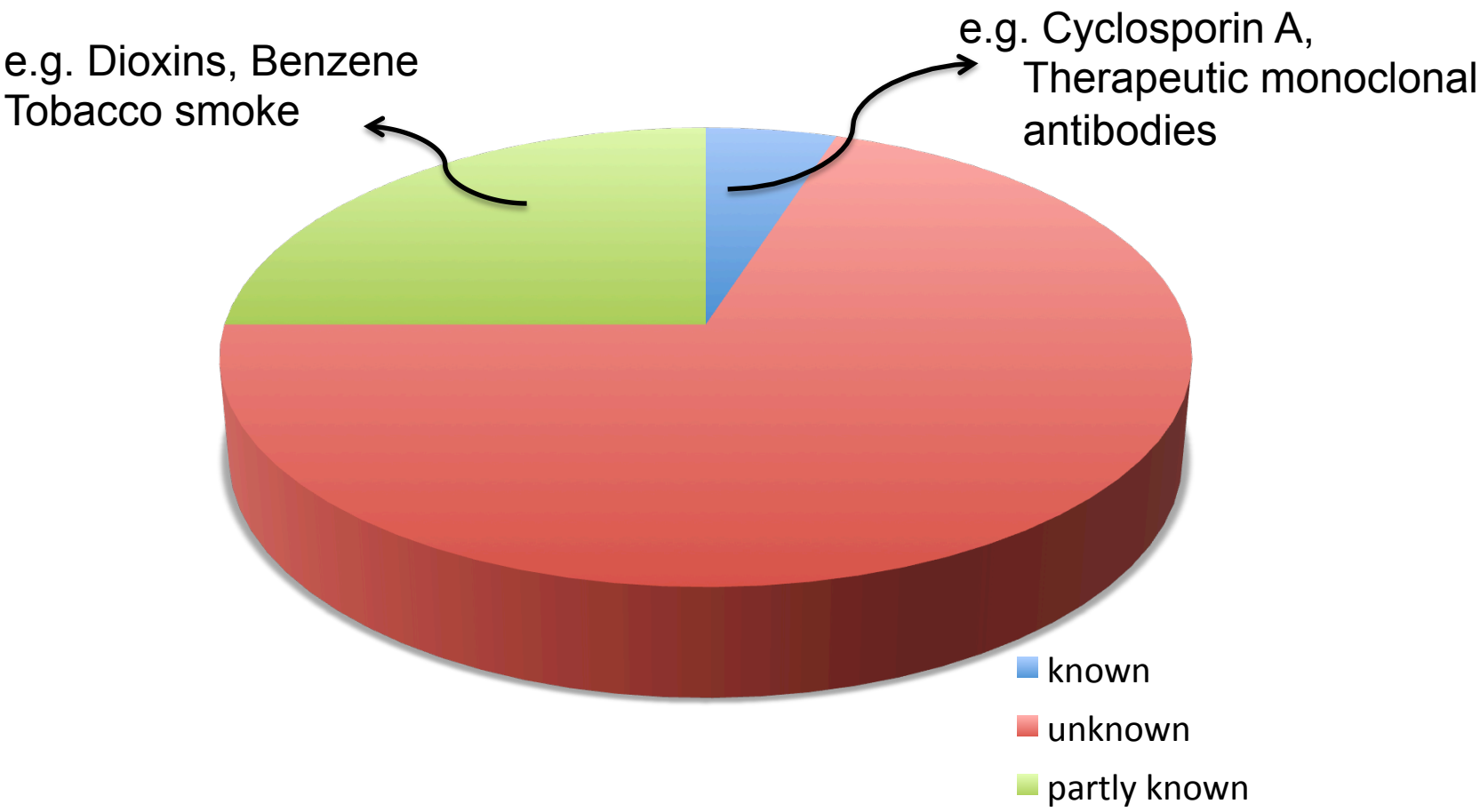
Government research

Is something immunotoxic?

What are the health risks?

Is there a safe level of exposure?

Chemicals for which we know something about how they modulate the immune system



Examples of exogenous chemicals that modulate the immune system

Inducers of Immunosuppression

- ✓ Pharmaceuticals (e.g. cyclosporin A, glucocortiocoids, chemoRx)
- ✓ Benzene
- ✓ Dioxins (TCDD) and some dioxin-like compounds
- ✓ Polyaromatic hydrocarbons (e.g., benzo(a)pyrene)
- ✓ Tobacco Smoke
- ✓ Illegal drugs (e.g. cocaine, cannabanoids)

Inducers of Hypersensitivity

- ✓ Many pharmaceuticals (e.g., penicillin)
- ✓ Nickel
- ✓ Thimerosal
- ✓ Latex rubber
- ✓ Food Proteins
- ✓ Formaldehyde
- ✓ Particulate pollutants (e.g., diesel exhaust particles)

Inducers of Autoimmunity

- ✓ Some pharmaceuticals (e.g., halothane)
- ✓ Trichloroethylene
- ✓ Mercury

Potential mechanisms of Immune Suppression

1. Loss of function or death of precursor cells
2. Blockage or skewing of cell signaling cascades
3. Preventing or deregulating cell differentiation
4. Inhibition of cell proliferation
5. Inhibition of immune cell function
6. Growth of the “wrong” cell type, or inappropriate secretion of cytokines or other regulatory factors
7. Incorrect or insufficient antigen presentation

Potential Mechanisms for Immune Enhancement

1. Failure or delay of down-regulatory mechanisms
2. Impaired cell death mechanisms
3. Uncontrolled cell proliferation, or proliferation of the “wrong” type of cell
4. Skewing of cell differentiation
5. Inappropriate secretion of cytokines or other regulatory factors
6. Recognition and response to self or harmless antigens
7. Trafficking of immune cells to restricted sites

There are a lot of ways to alter the function of the immune system!*

- ✓ Changing the proliferation and differentiation of immune cells
  - Progenitor cell types
  - Mature peripheral leukocytes
- ✓ Changing cellular trafficking
- ✓ Changing signal transduction cascades
- ✓ Dysregulation of tolerance mechanisms
- ✓ Changing antigen processing and presentation
- ✓ Increasing or decreasing cell death mechanisms
- ✓ Changing the cytokines, chemokines, adhesion molecules and/or their receptors, enzymes, free radicals…… expressed on or secreted by immune cells

***and they are not mutually exclusive**

How do environmental chemicals influence immune responses to infectious agents?

Genetics & Epigenetics

Infectious disease

Age

Environmental Exposures

Images: www.cdc.gov, www.ohbaby.co.nz, www.geography.hunter.cuny.edu, www.heatlthhype.com

Many endocrine disrupting chemicals (EDCs) bind nuclear receptors

Steroid hormone receptor family
Estrogen receptors (ERs)
Androgen receptor (AR)
Glucocorticoid receptor (GR)

Heterodimeric nuclear receptors
Peroxisome-proliferator-activated receptors (PPARs)
Thyroid hormone receptor (TR)
Liver X receptors (LXR)

Monomeric nuclear receptors
Retinoid-related orphan receptors (RORs)
Steroidogenic factor like (SF1)
COUP-TFII

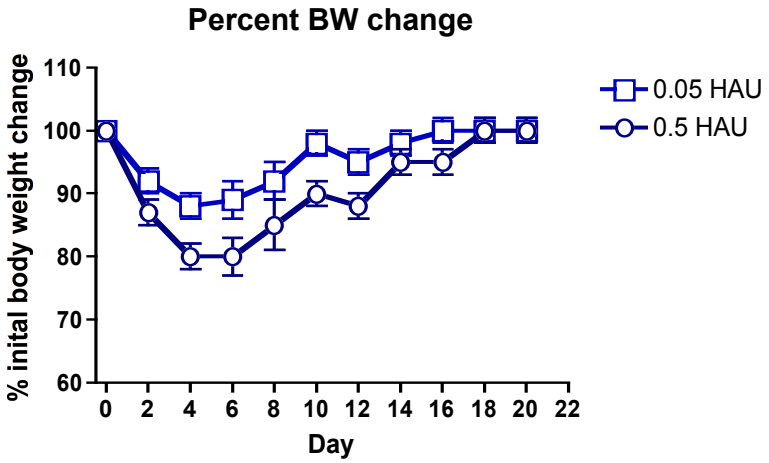
PAS family
AHR
HIF1α
CLOCK
BMAL
Per
Sim

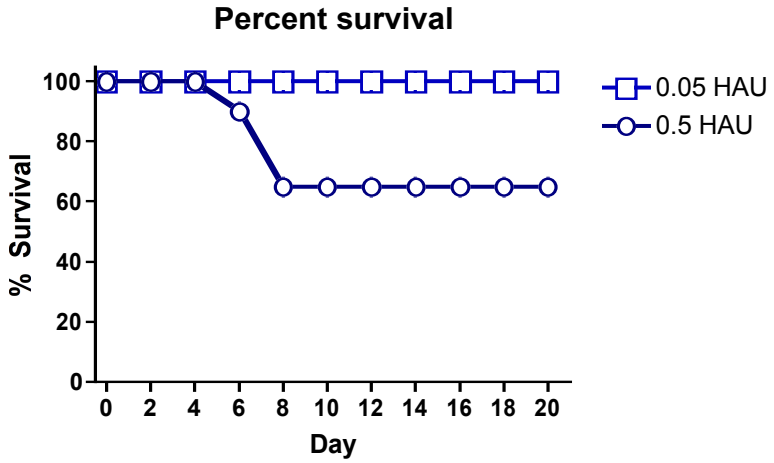
Why do we care about the AHR?

- ✓ The aryl hydrocarbon receptor (AHR) is a ligand-activated transcription factor that binds hundreds of chemicals
- ✓ Cells of the immune system express the AHR
- ✓ Chemicals (ligands) that bind to the AHR are "good" and "bad," and both types of ligands influence many aspects of immune function in adult animal models
- ✓ We don't yet understand role of the AHR in normal immune system development and function
- ✓ Environmentally-derived AHR ligands cross the placenta and accumulate in breast milk
- ✓ Recent epidemiology studies suggest AHR binding pollutants affect the human immune system

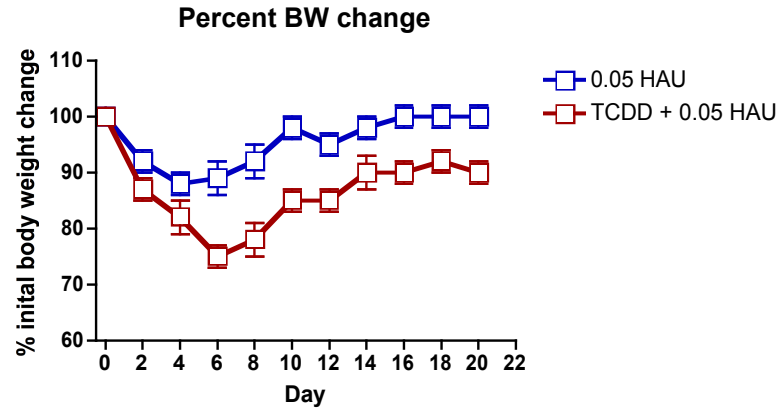
Exploring the effects of AHR binding pollutants on the immune response to respiratory viral infection

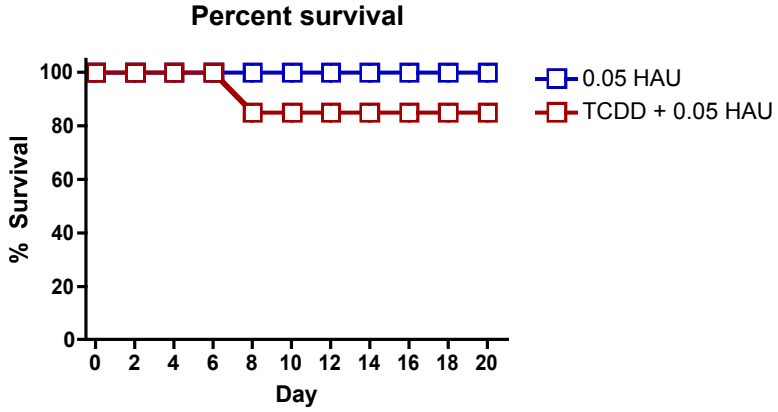
Increasing viral dose enhances severity of infection





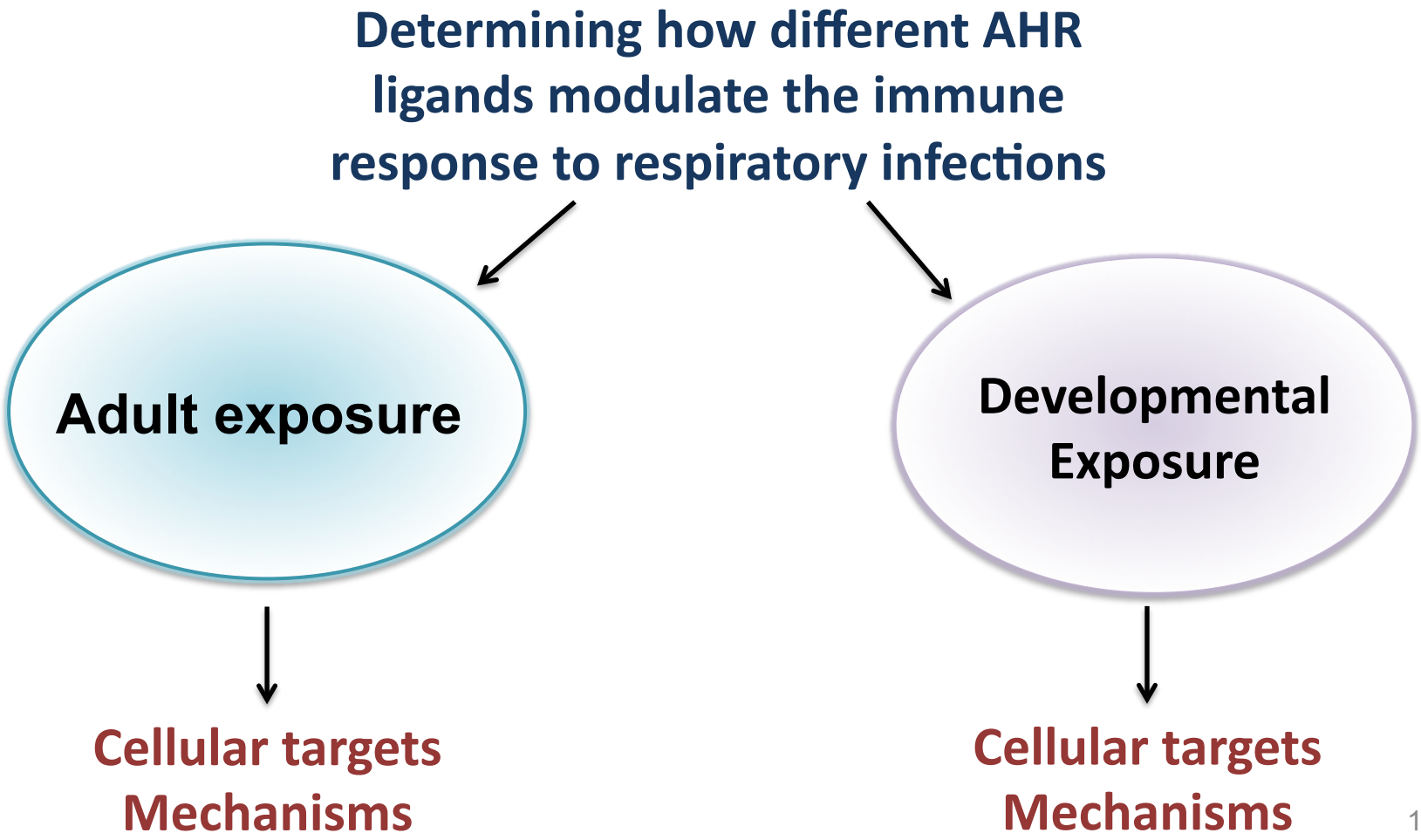
AHR activation enhances the severity of infection



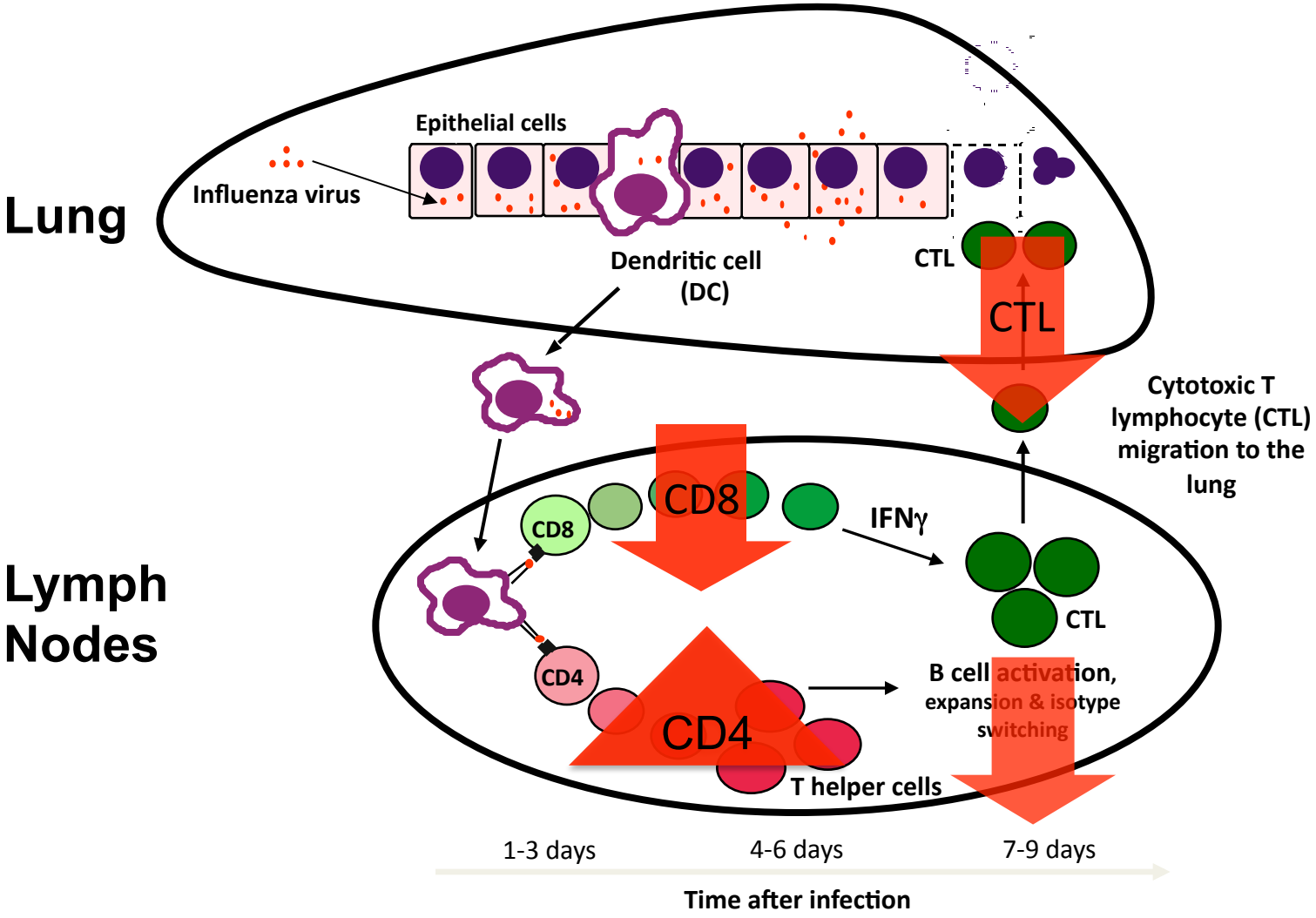


Lawrence & Vorderstrasse (2013)

Studying the effects of AHR activation on the immune response to respiratory viral infection



Some key findings: Both direct and developmental AHR activation disrupts the immune response to influenza A virus



Adapted from Head and Lawrence (2009)

Implications and Significance

Environmental chemicals may alter vulnerability to clinically severe outcomes of infection