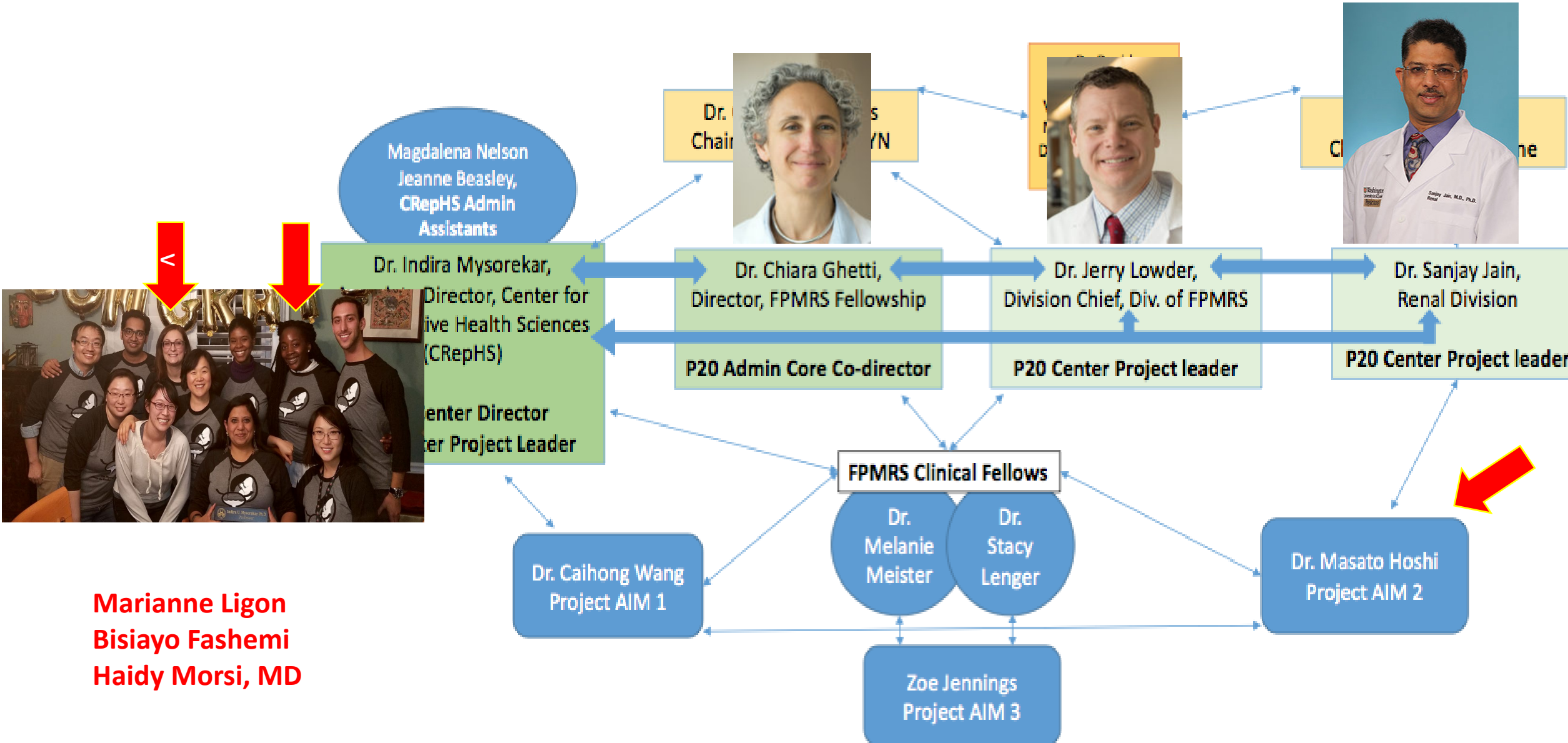


Cystitis cystica and recurrent UTIs in postmenopausal women

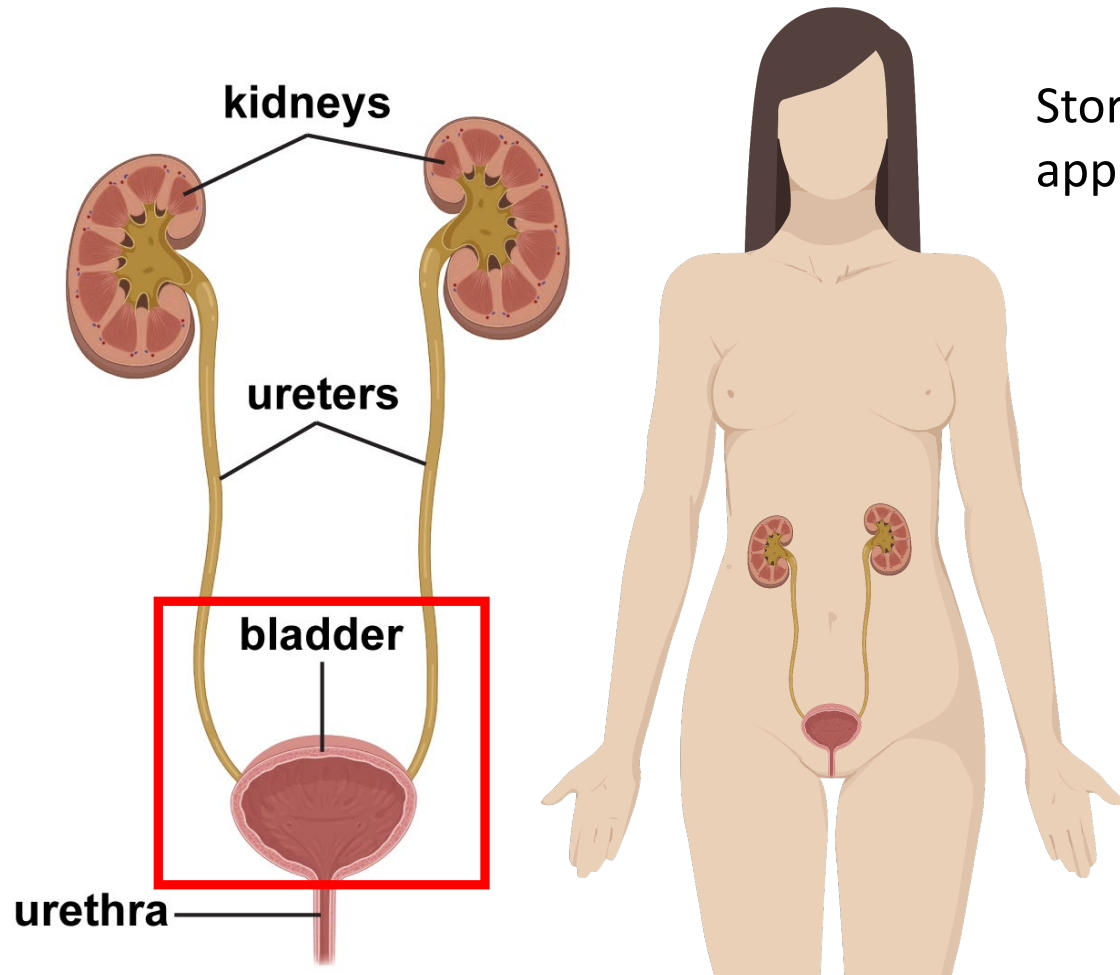
Indira U. Mysorekar, PhD
James P. Crane Professor of Obstetrics & Gynecology;
Pathology & Immunology
Chief, Division of Basic Research,
Director, Centre for Reproductive Health Sciences
Washington University School of Medicine
St. Louis, MO



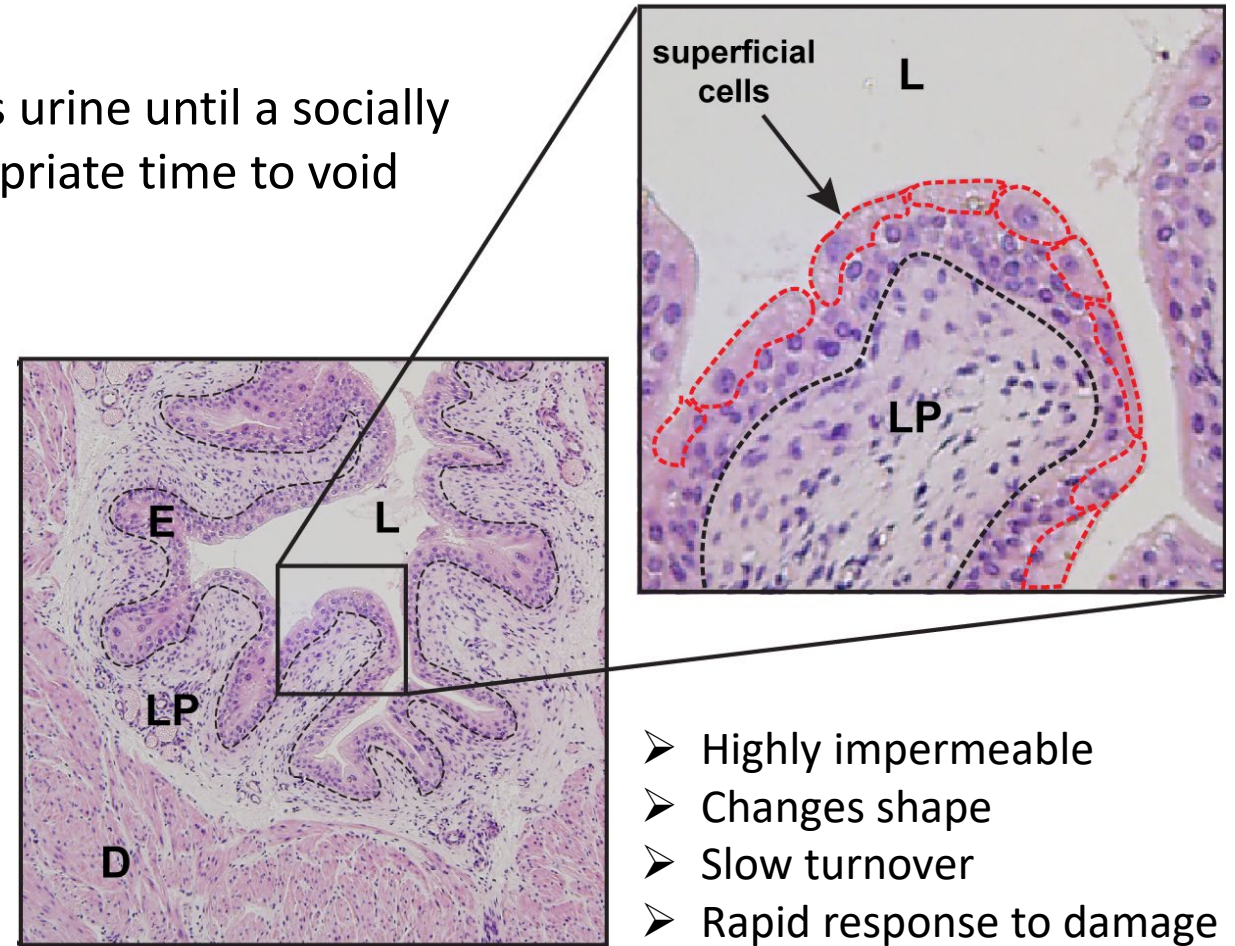
WASHINGTON UNIVERSITY P20 DEVELOPMENTAL CENTER FOR INTERDISCIPLINARY RESEARCH IN BENIGN UROLOGY



The Urinary Bladder and Urothelium

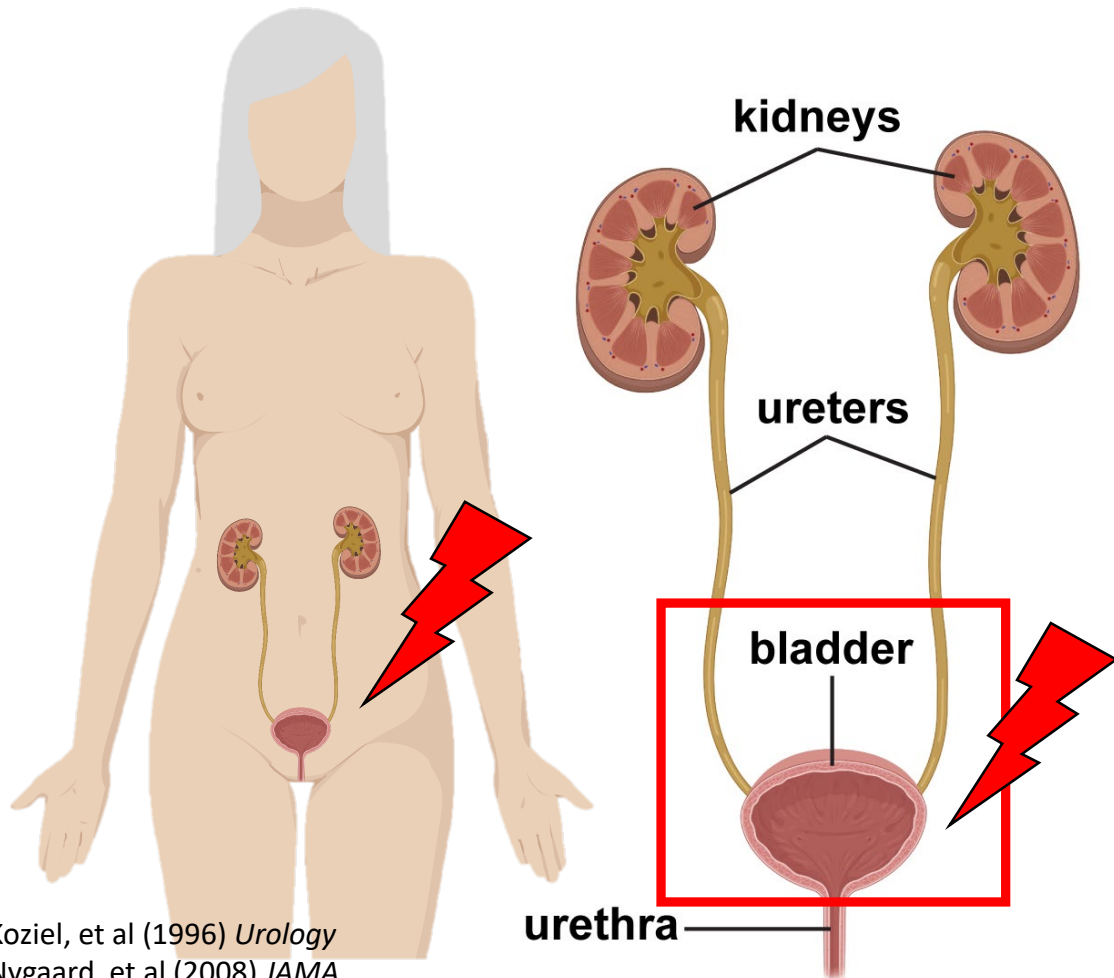


Stores urine until a socially appropriate time to void



- Highly impermeable
- Changes shape
- Slow turnover
- Rapid response to damage

Urinary tract conditions and diseases worsen with age



➤ Recurrent urinary tract infection (rUTI)

Interstitial cystitis/bladder pain syndrome (IC/BPS)

- Sterile inflammation
- Barrier dysfunction
- **Most often diagnosed in 40s**

50% of women over 65 have incontinence

Overactive bladder/urge incontinence (OAB)

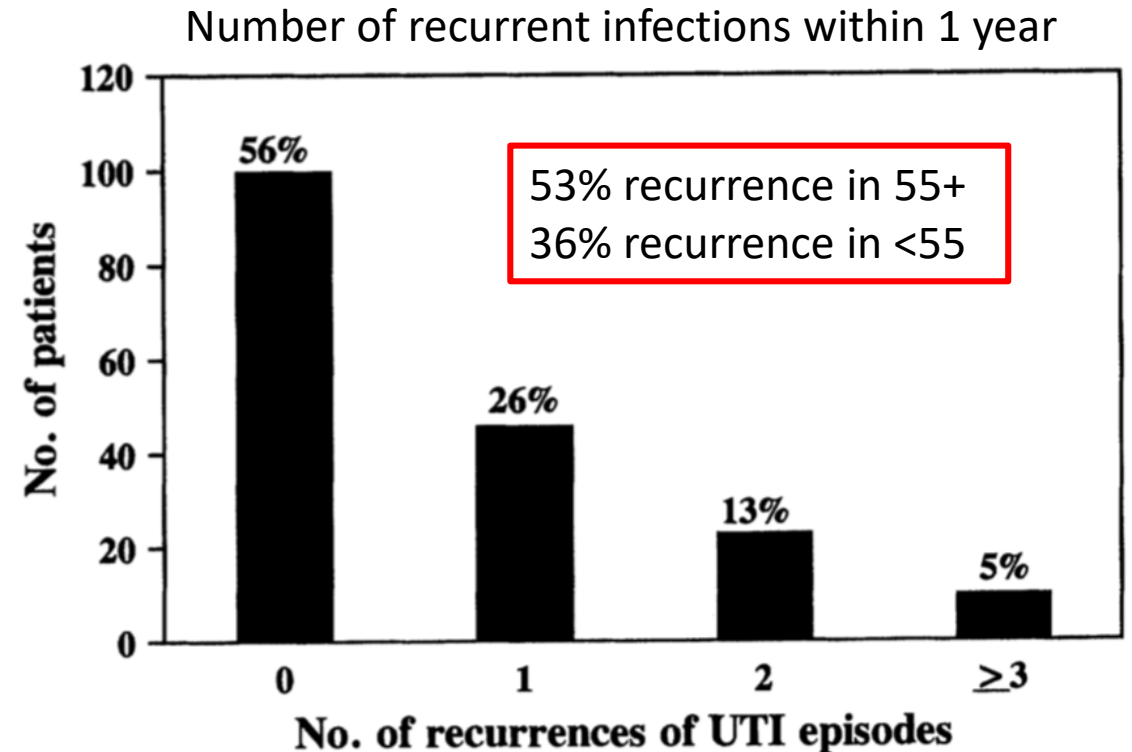
- “Non-inflammatory”
- Leakage with urge
- Overactive detrusor muscle

Stress incontinence

- Leakage with coughing, laughing, sneezing, etc.
- Weakness or spasm of pelvic floor muscles

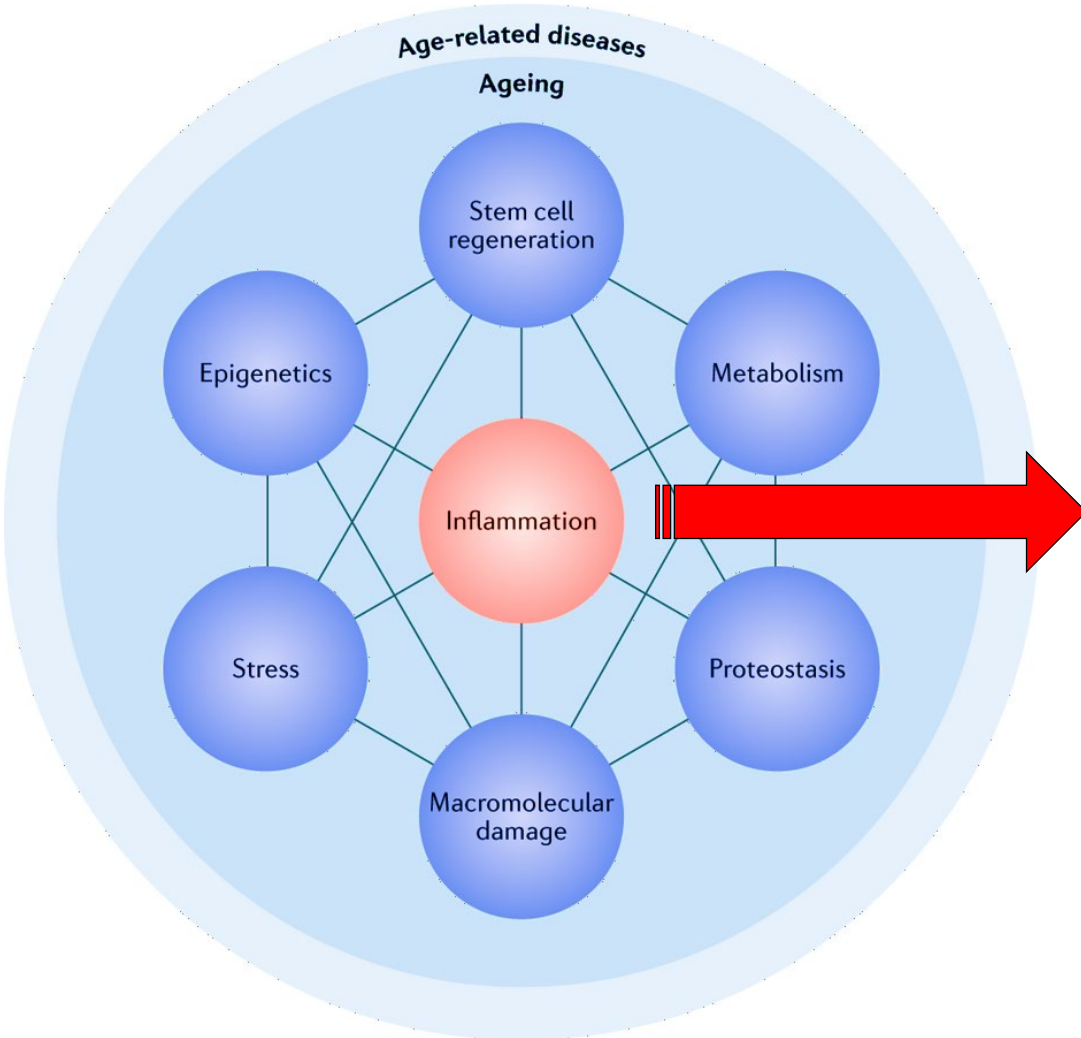
Urinary tract infections (UTIs)

- Most common infectious disease in women (>50% lifetime risk)
- Economic burden >\$2 billion annually in US
- Most common reason for outpatient antibiotic prescription
- 20-50% become recurrent UTIs (rUTI)
 - Repeat infection within 6 months of initial infection
 - Despite appropriate antibiotic treatment
 - **Women 55+ have ~50% recurrence**



Ikaheimo, et al. 1996. *Clin Infect Dis*

“Inflamm-aging”



Protective

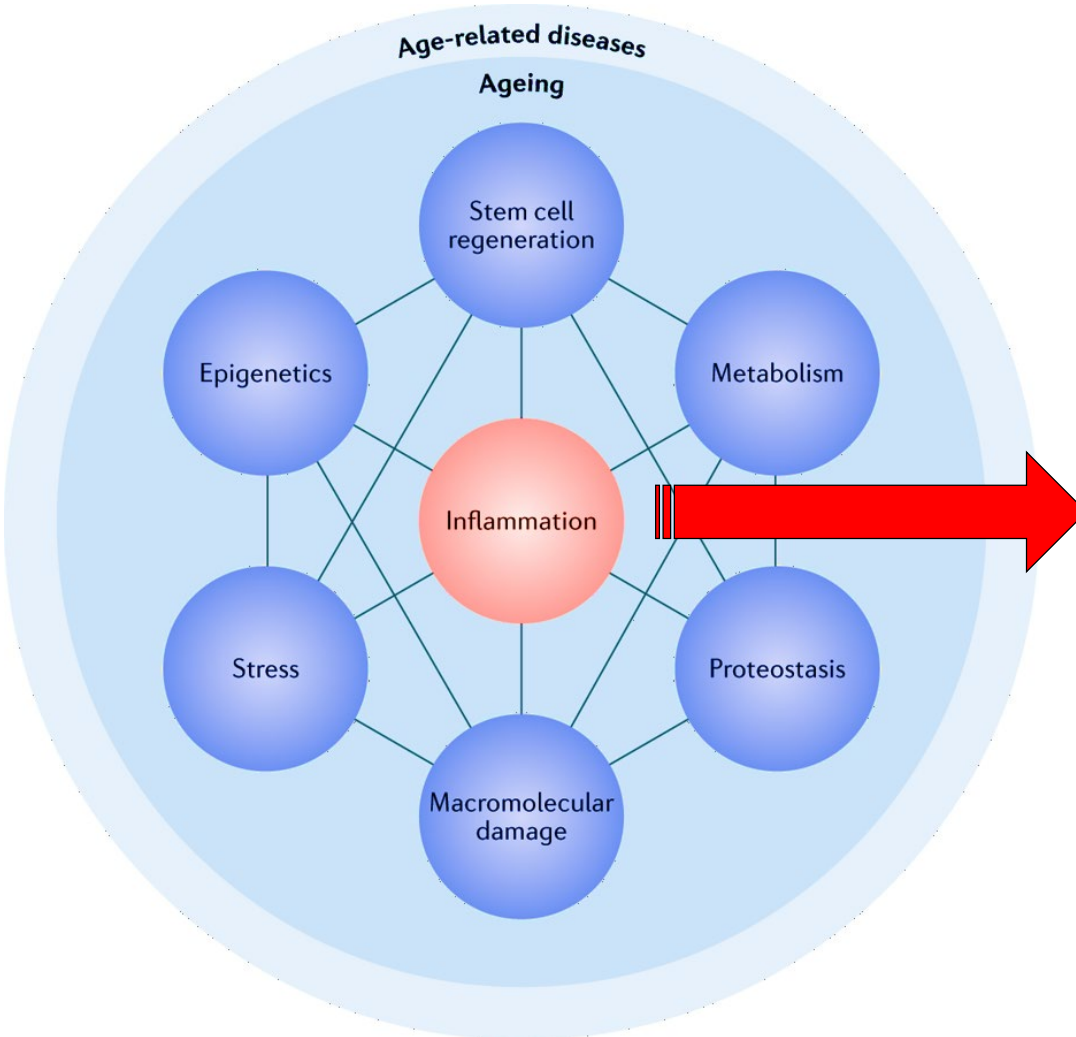
- Protection from pathogens
- Response to vaccines
- Control of chronic/latent infections
- Removal of mutated cells

Pathogenic

- Chronic inflammation
- Autoimmune/inflammatory disease
- Tissue degeneration
- Pro-tumorigenic

Immune System

“Inflamm-aging”

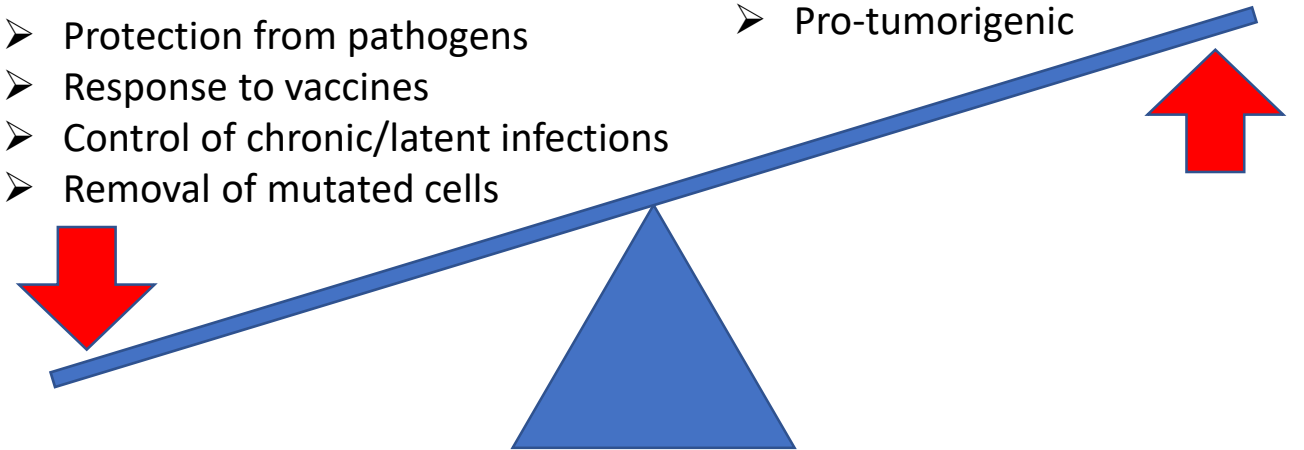


- Protective**
- Protection from pathogens
 - Response to vaccines
 - Control of chronic/latent infections
 - Removal of mutated cells



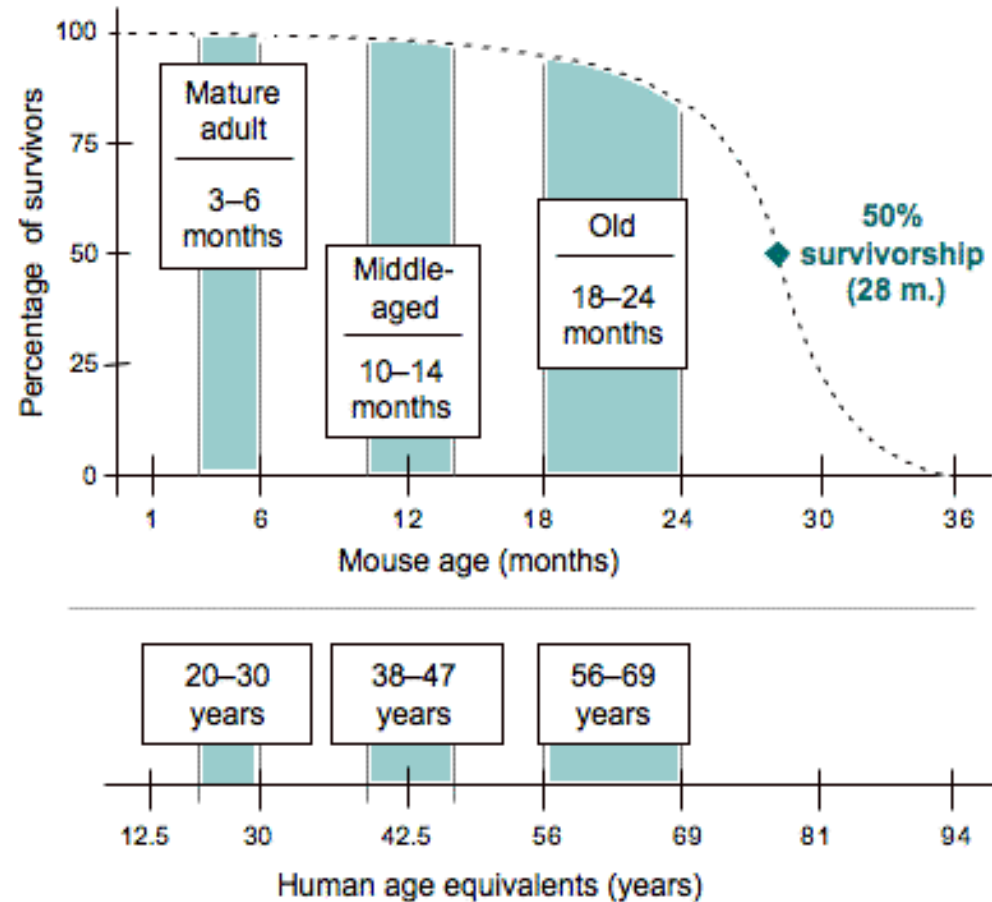
Pathogenic

- Chronic inflammation
- Autoimmune/inflammatory disease
- Tissue degeneration
- Pro-tumorigenic



Mouse model of aging

Life phase equivalencies



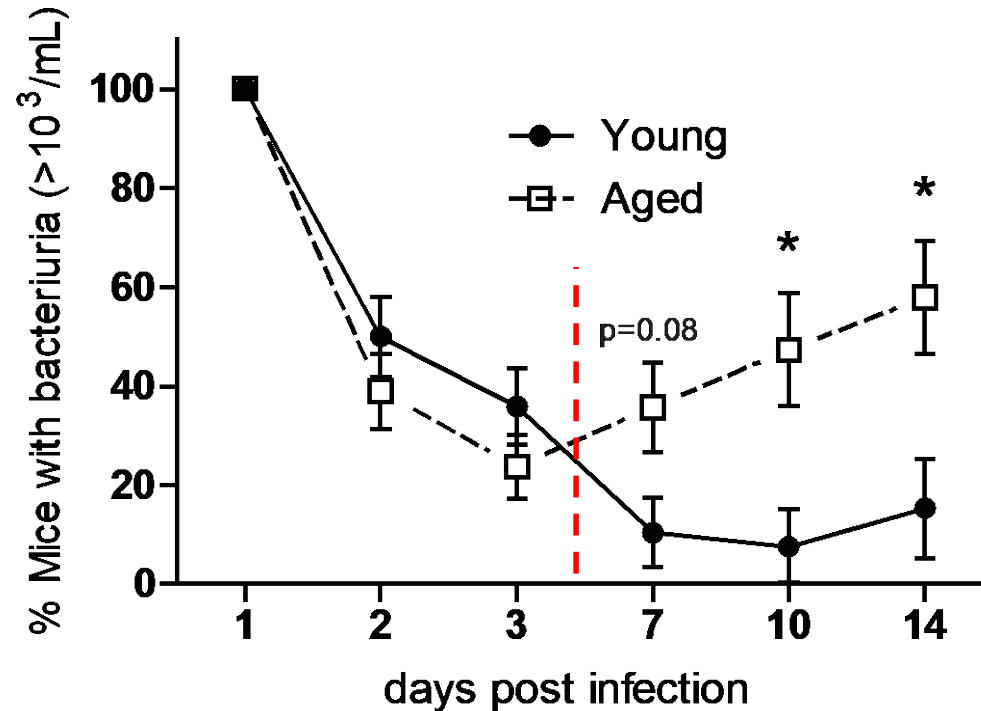
Young mice – 2-4 months

Aged mice – 18-22 months

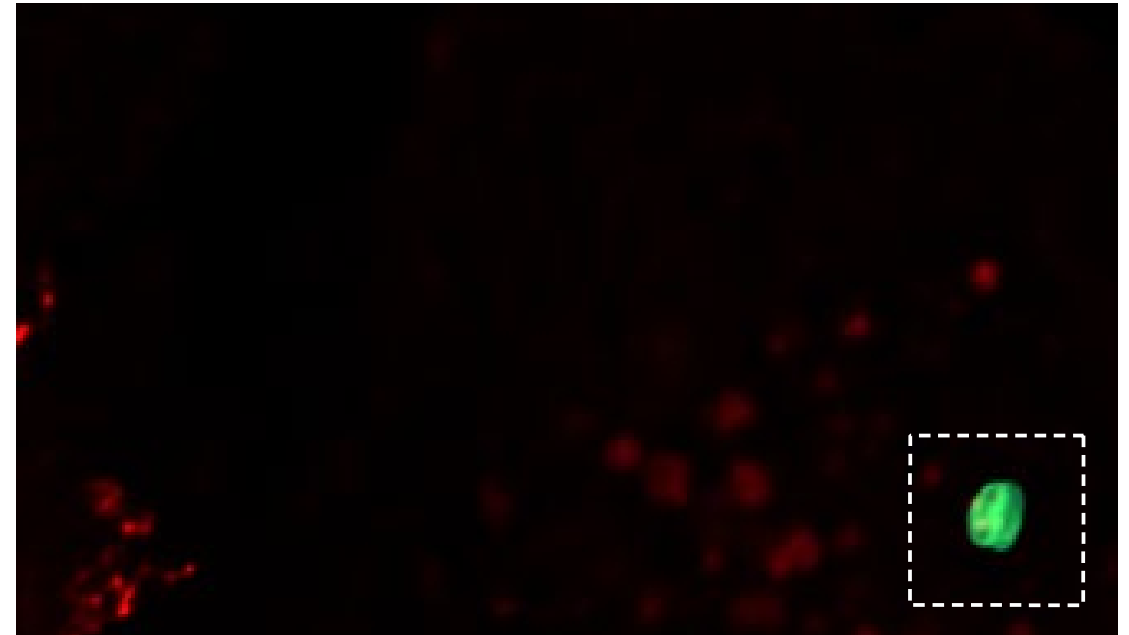


Aged mice have frequent UTI recurrences and enhanced QIR formation

Aged mice have spontaneous rUTI phenotype



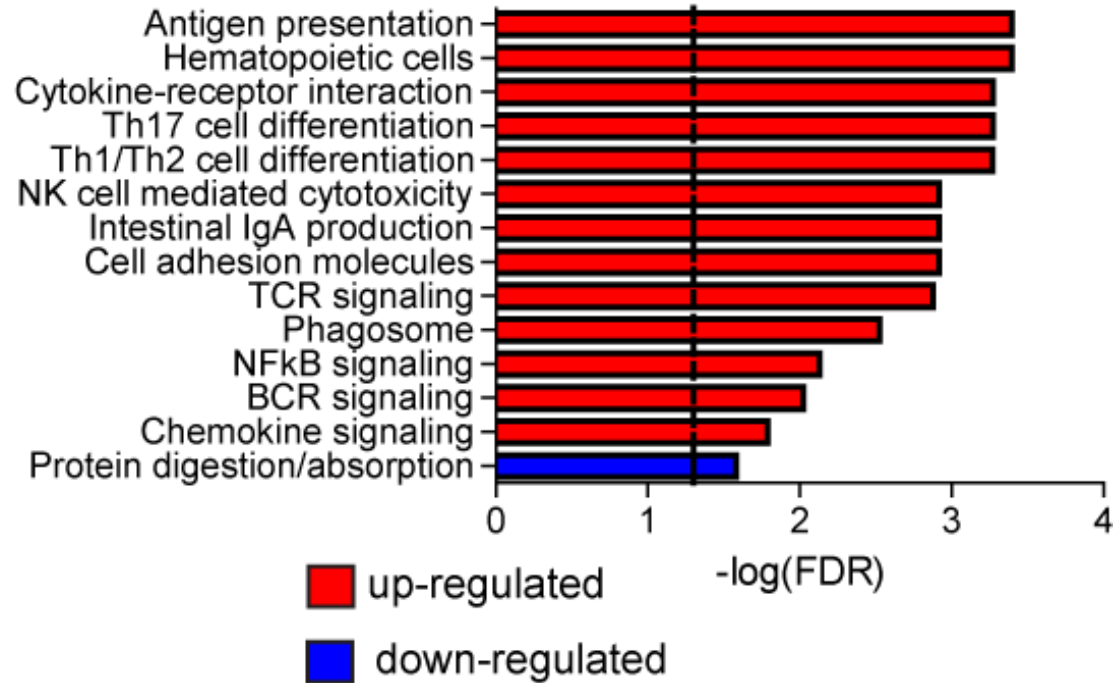
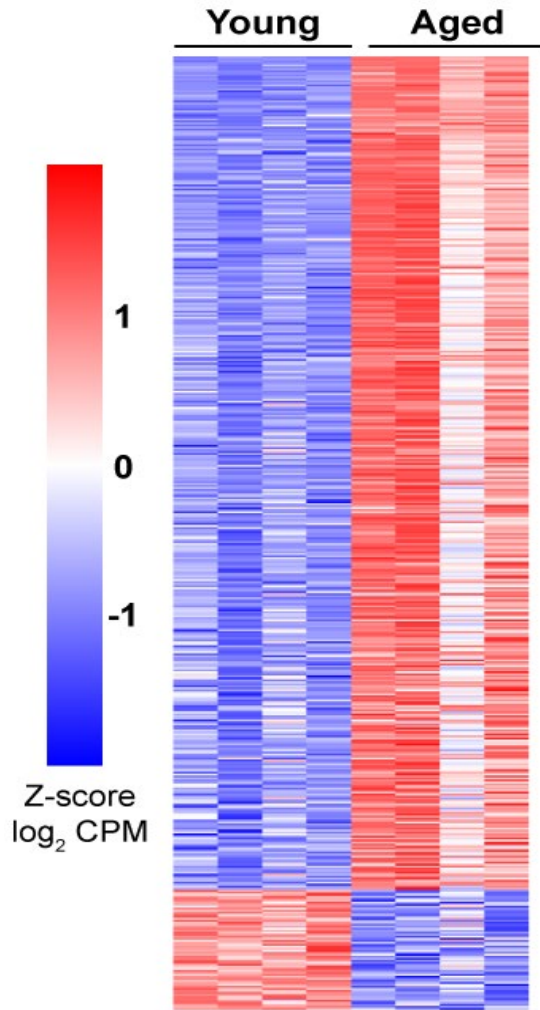
Large QIR in aged mice



RNA-sequencing reveals highly altered aged bladders

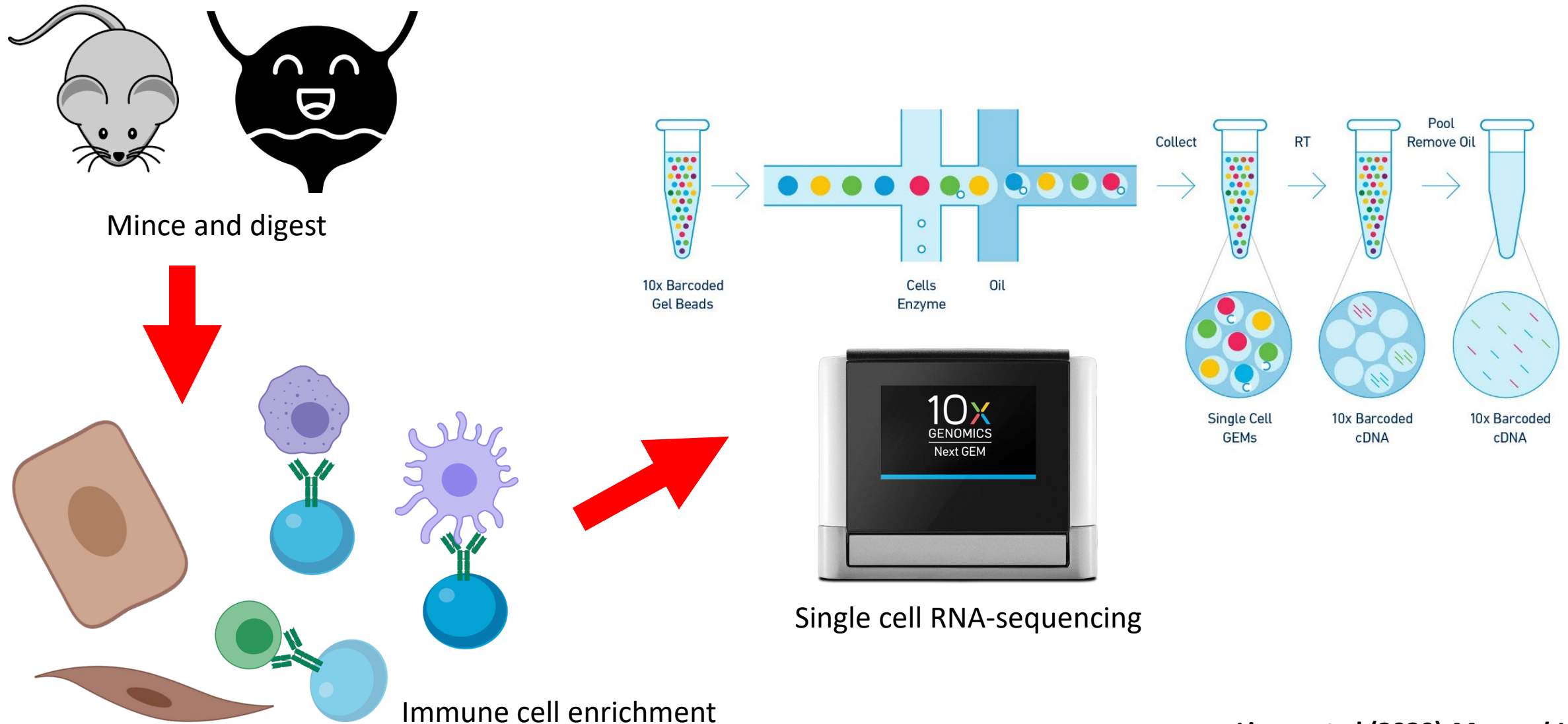
417 genes

>2-fold change,
FDR-adjusted
 $p < 0.05$

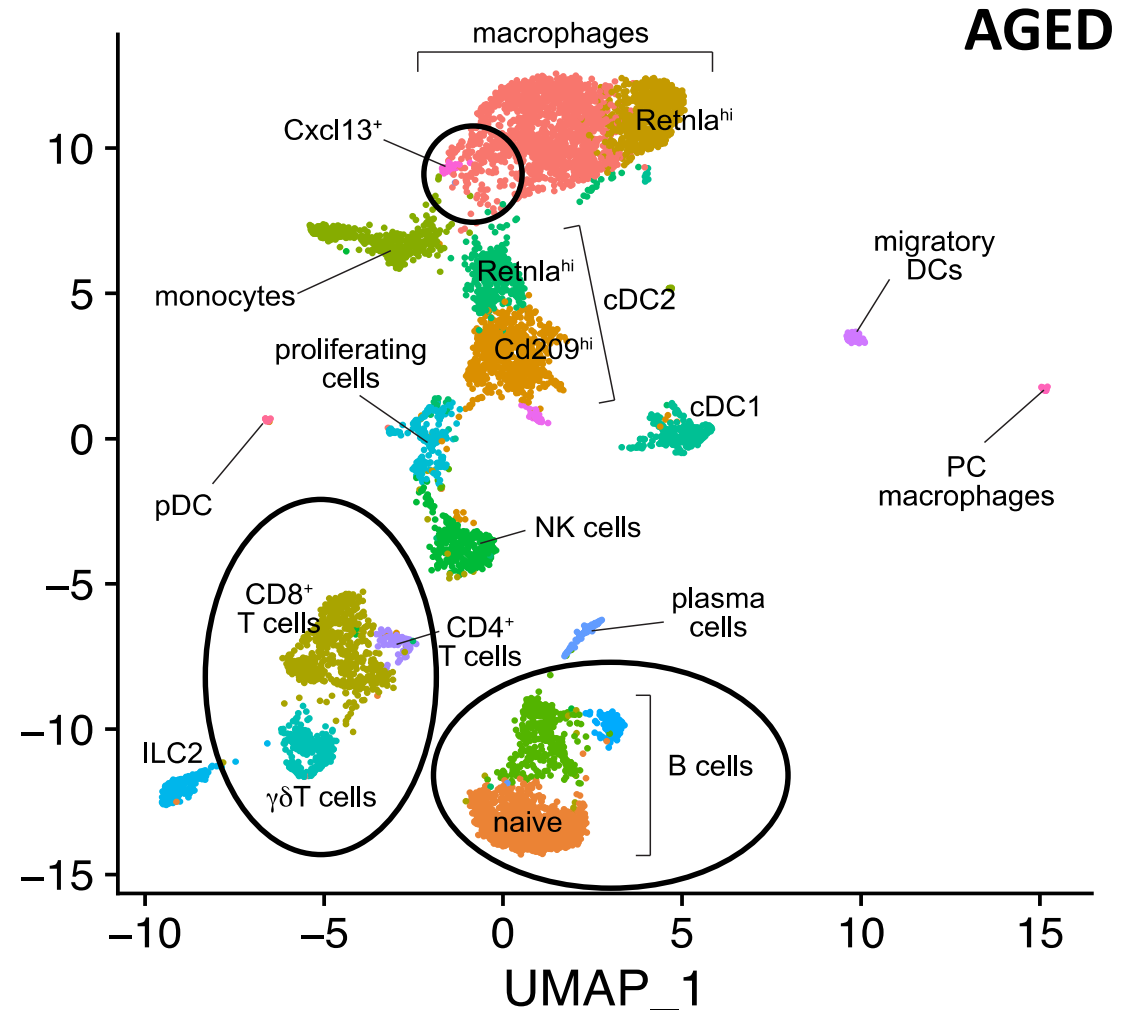
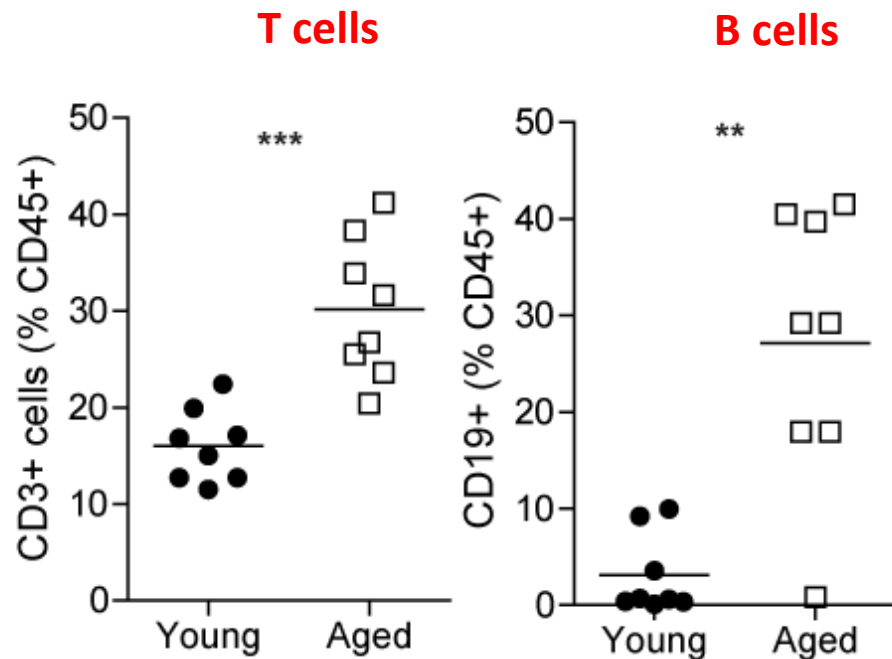


Dr. Marianne Ligon
MSTP

Enrichment of Bladder Immune Cells for scRNA-seq



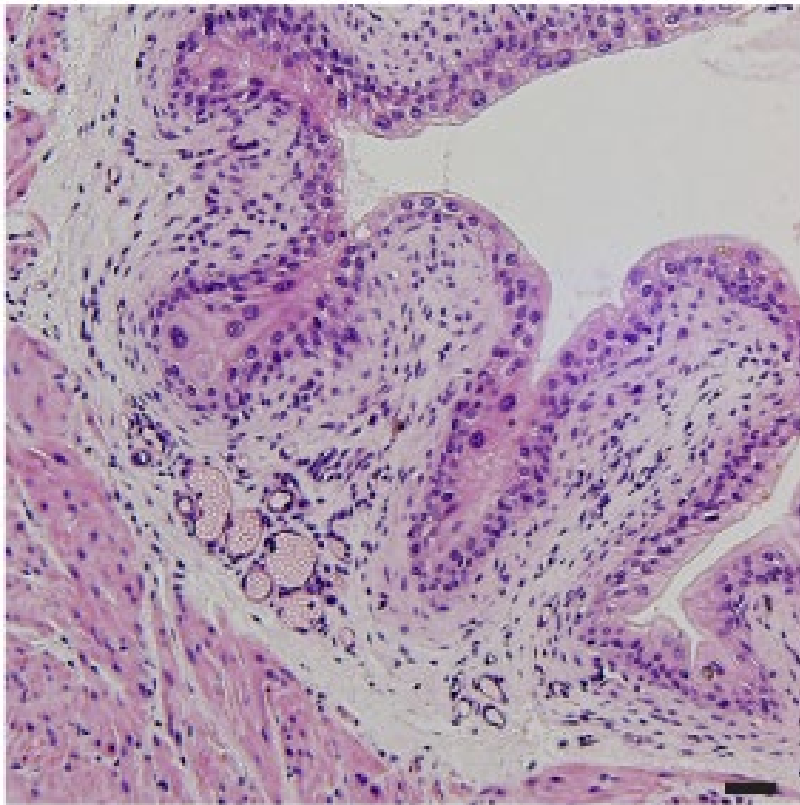
Lymphocytes displace macrophages as the predominant immune cell in the aging bladder



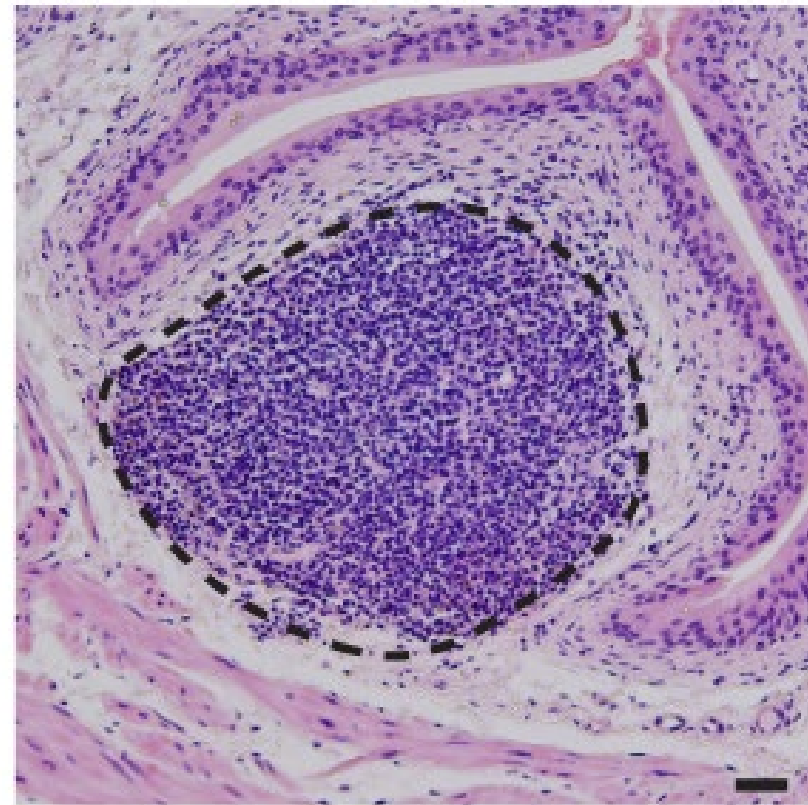
Ligon, et al (2020) *Mucosal Immunol*

Lymphocyte accumulation in aged bladders

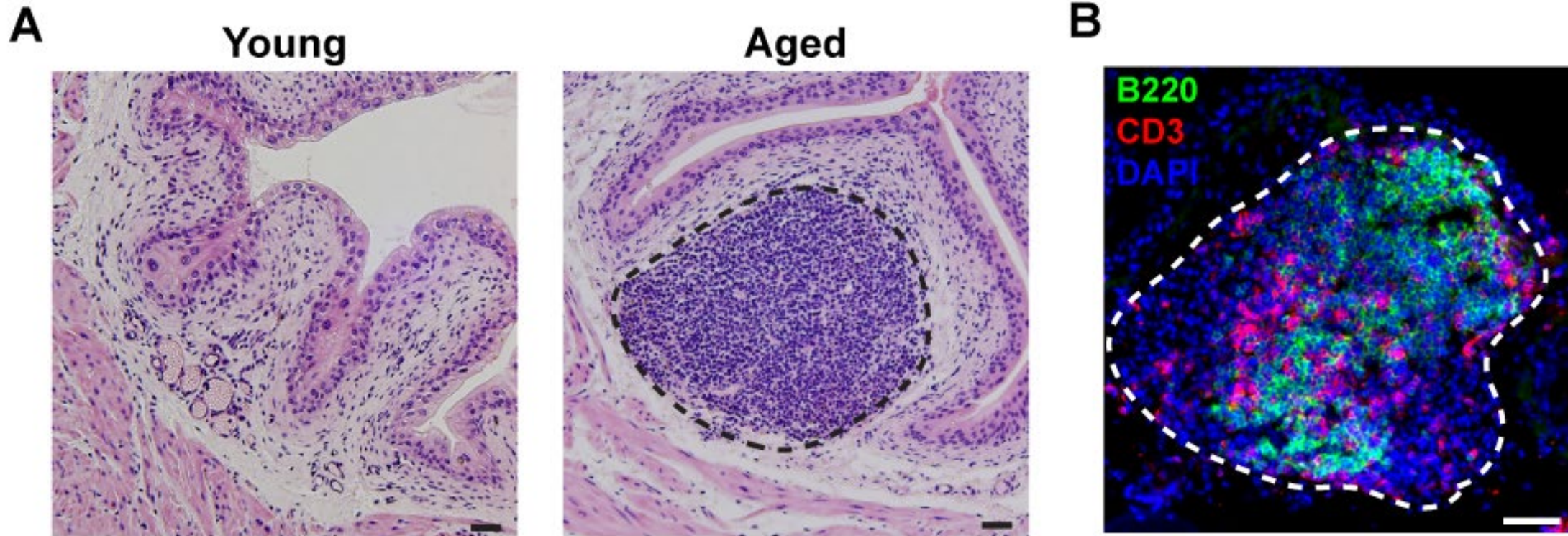
Young



Aged

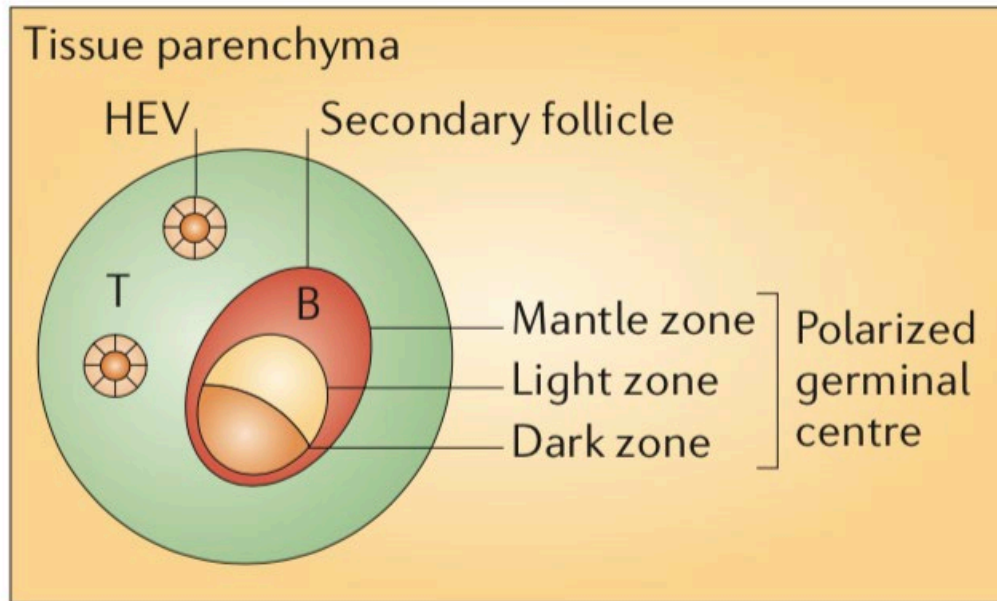


Lymphocytes localize to distinct aggregates in bladders from aged mice



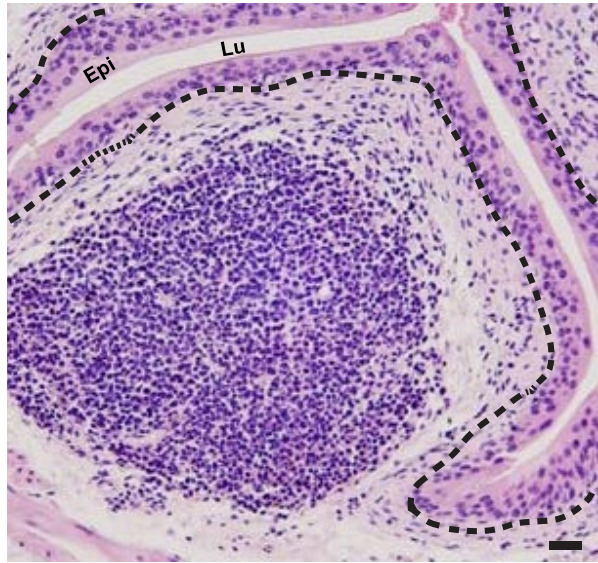
Structure suggests bladder tertiary lymphoid tissues (BTLT)

Tertiary Lymphoid Tissues (TLTs)

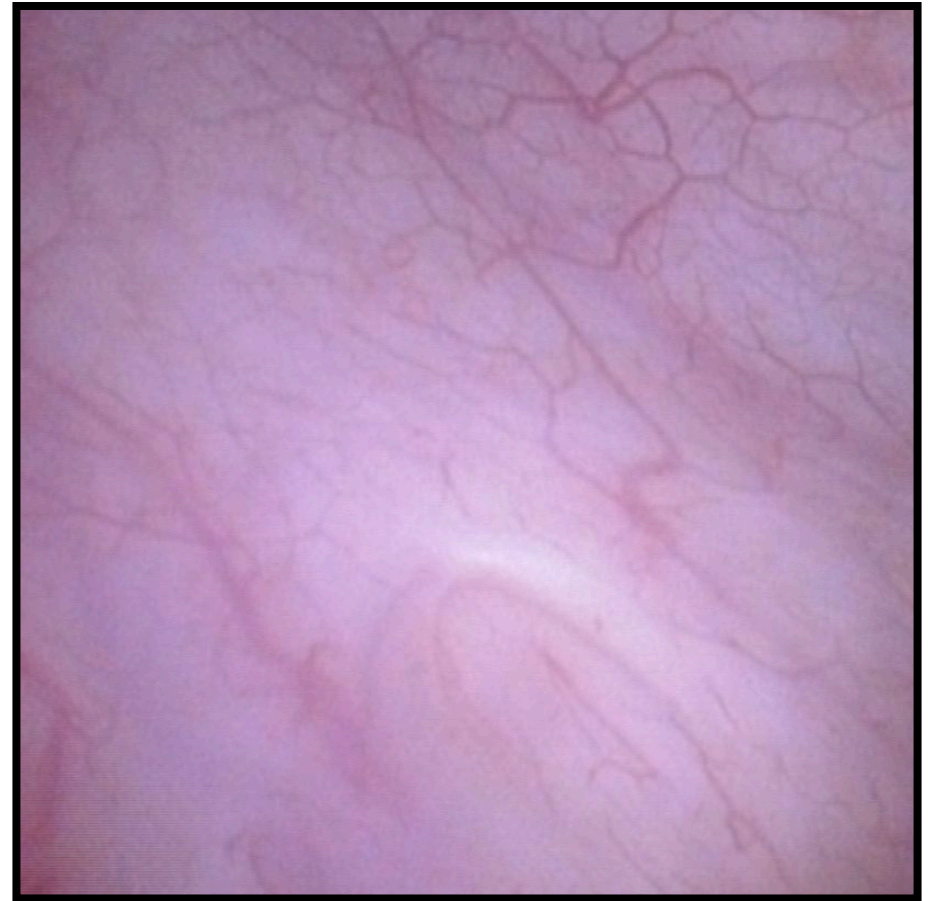
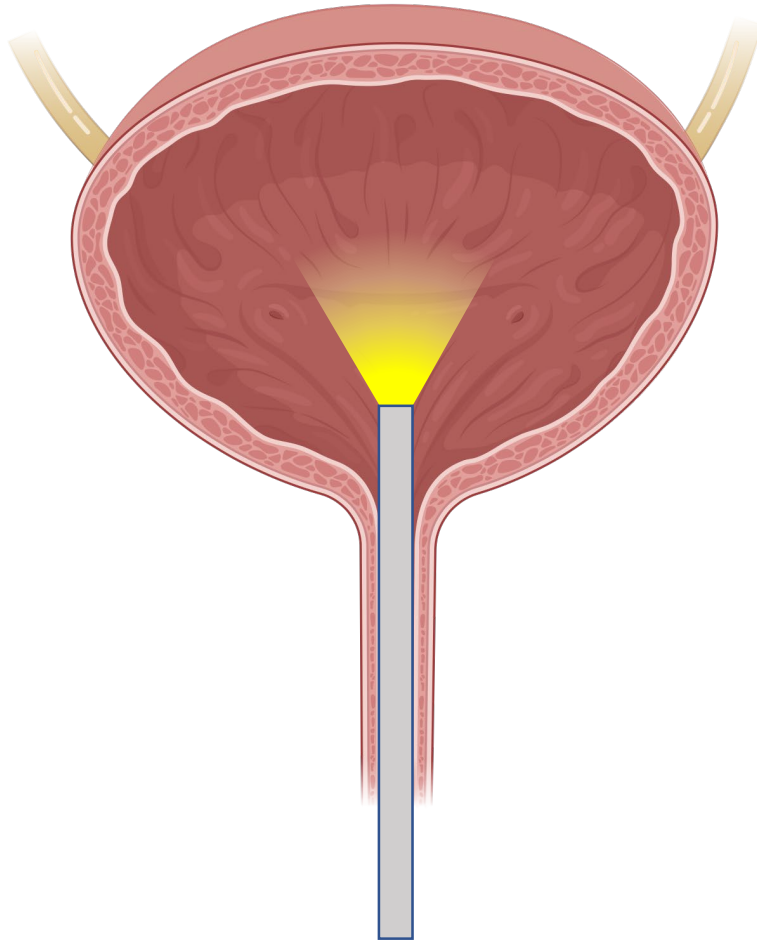


- Resemble structure & organization of SLOs
- Form ectopically in chronically inflamed tissues
- Play a role in local immune responses
 - Autoimmunity, cancers, chronic infections, atherosclerosis
 - Pathogenic vs. protective?

Lymphoid follicle formation increases with age



Cystoscopy in rUTI patients

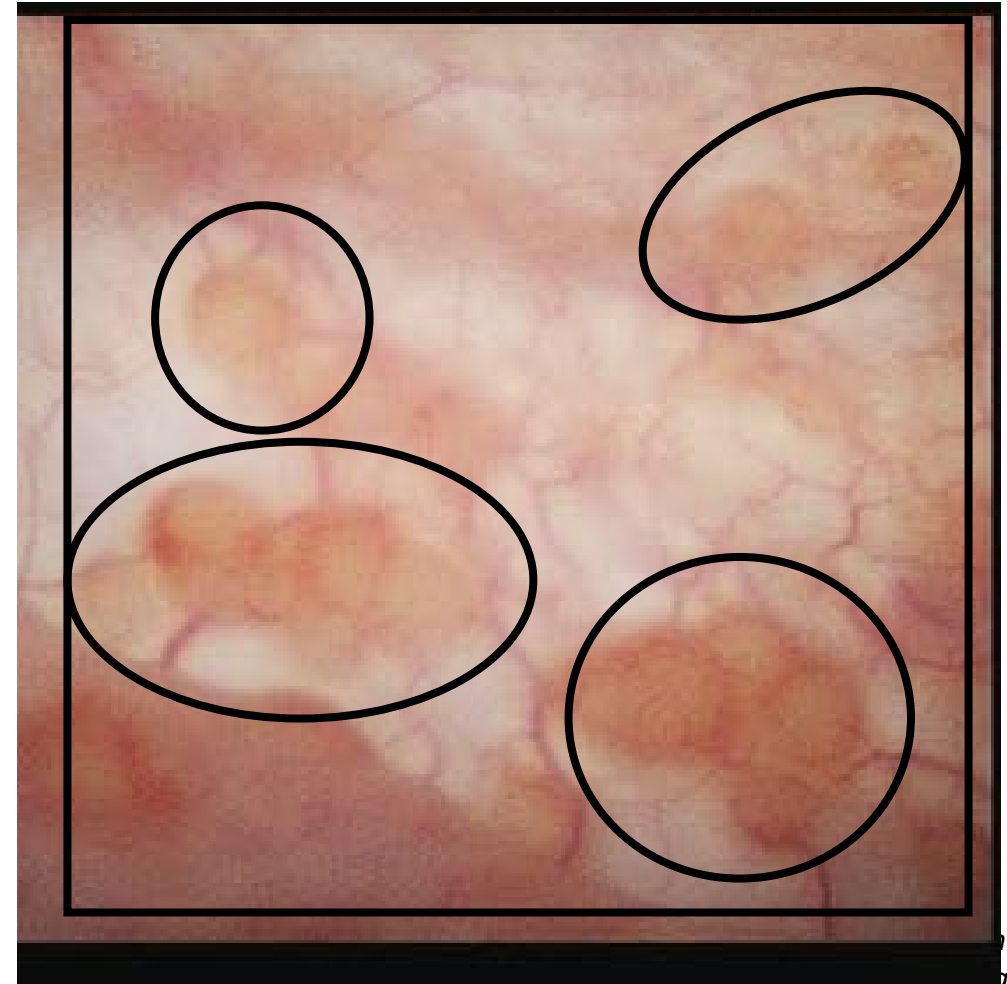


Normal bladder

Cystitis cystica (CC)

- Small red, yellow, to gray nodules observed on cystoscopy
- Incidental, non-specific chronic inflammation, non-malignant
- Lack of sufficient literature on CC
 - Unknown epidemiology, pathogenesis, or significance (other than “chronic inflammation”)

Are CC nodules are similar to bTLT seen in aged mice?



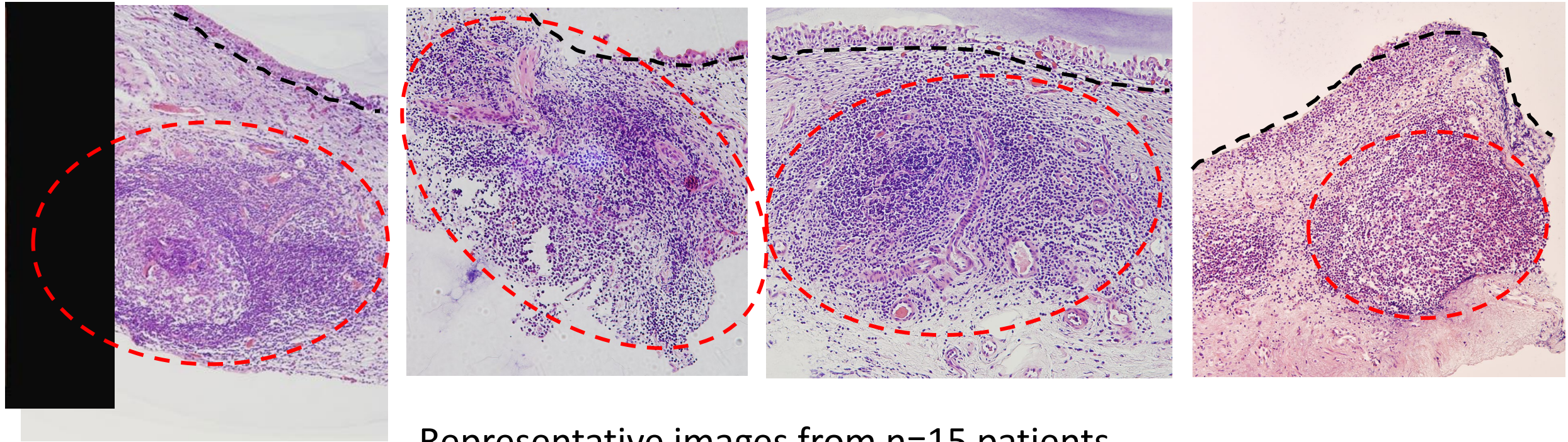
es: Bladder.

glad lekarshi

Marsh FP, et al (1974) *J Clin Path*

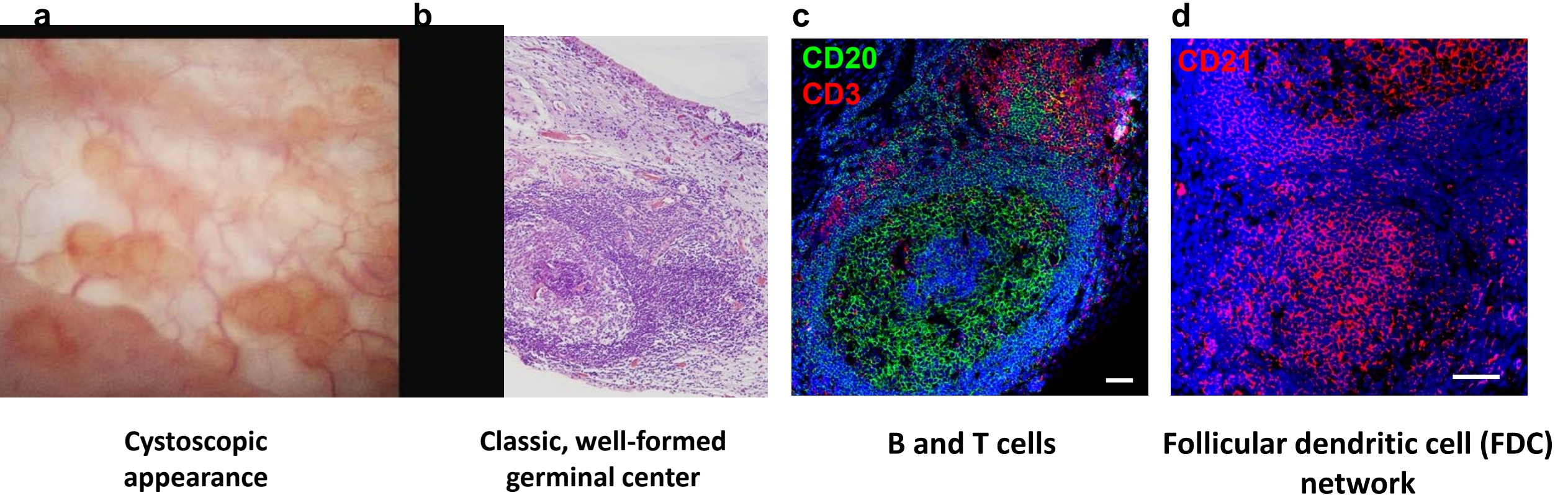
Walters & Karrem (2015) *Urogynecology & Reconstructive Surgery*

CC biopsies contain bTLT



Representative images from n=15 patients

CC biopsies resemble mouse bTLTs



Unpublished



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FUNDING

NICHD R01-HD091218
NIDDK R01-DK100644
NIA R01-AG052494B
NIDDK P20 DK097798
NIA-R56 AG064634
NICHD RADx-UP



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