Mucosa/Submucosa Remodeling in Aging

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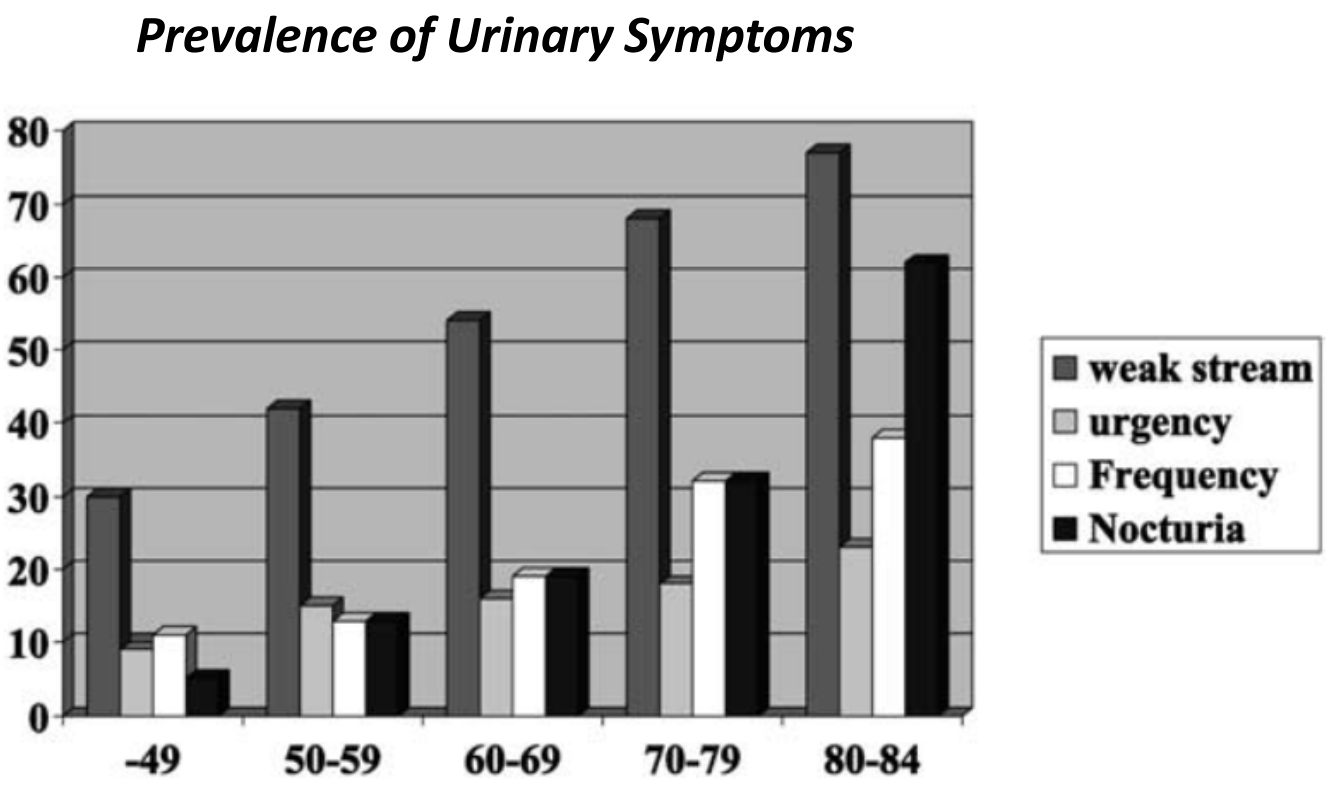
Prevalence of a number of urinary bladder disorders—increases with age



C. E. Dubeau, "The aging lower urinary tract.," J. Urol., vol. 175, no. 3, pp. 11–15, 2006.

Significance: The process of 'aging' can lead to changes in bladder structure and function - and this can be influenced by remodeling

Young 'healthy'

Vascular

Biomechanical

Remodelling

Immune Systems

Neurological

Aged 'unhealthy'

State of the Art Knowledge / Gaps

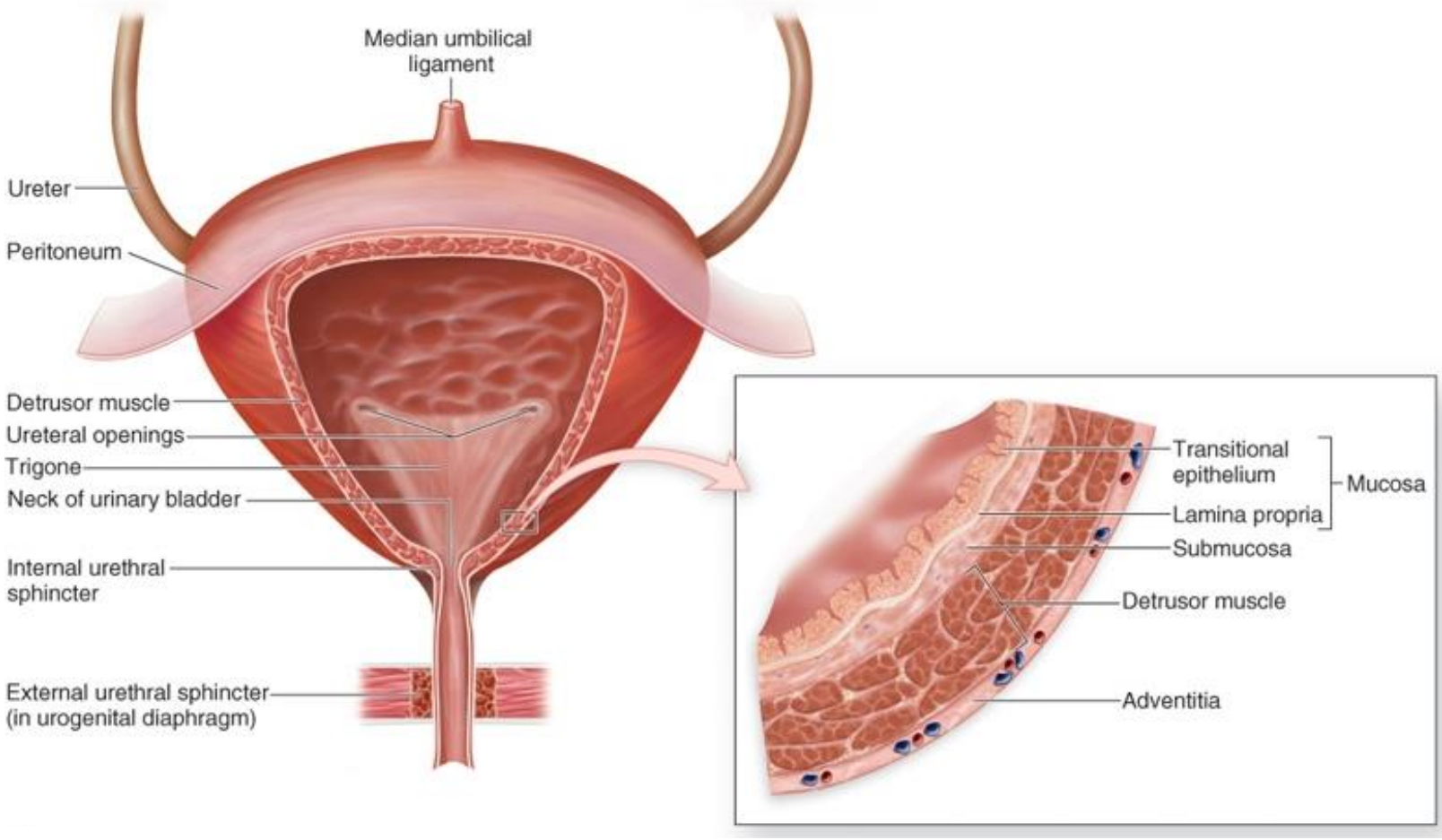
Age-related dysfunctions in the bladder *(i.e. fibrosis*) can make the elderly more vulnerable to developing incontinence

Mechanisms proposed to explain voiding dysfunction in the elderly include collagen deposition / fibrosis

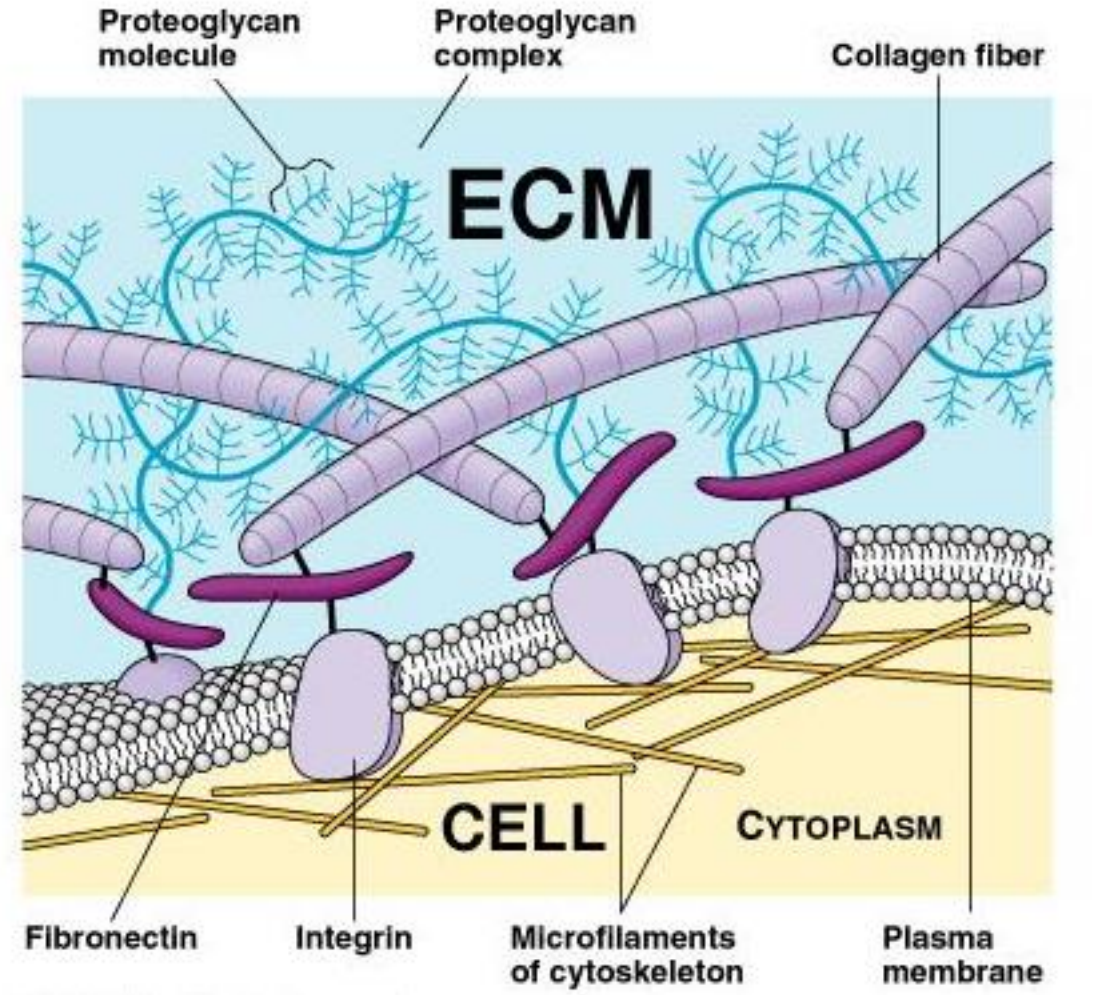
The causes of fibrosis remain unknown- however may involve ischemia and oxidative stress

Urinary Bladder- made up of multiple layers/cell types

Along with smooth muscle- the complex network of the *extracellular matrix (collagen / elastin)*-forms the primary load bearing structural components of the bladder wall

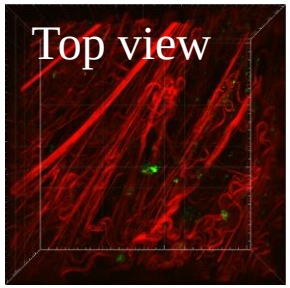


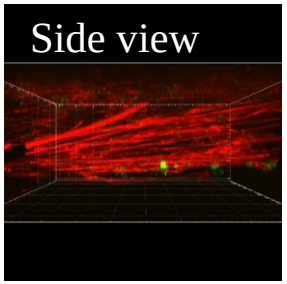
The extracellular matrix (ECM)- allows mechanical deformations to occur during bladder filling/emptying- provides structural support

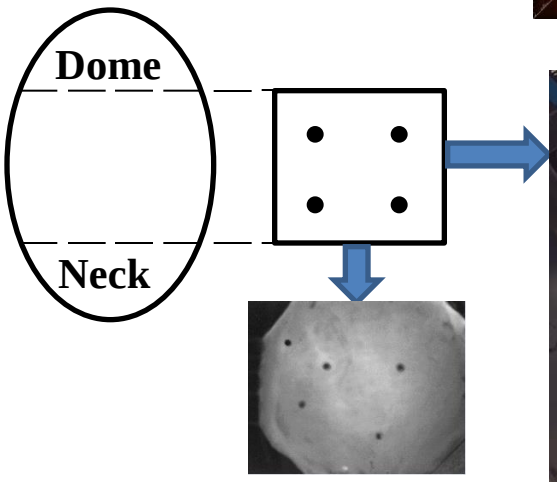


In pathology and aging- there is a loss of organization and function of the extracellular matrix- limited understanding as to cause/effect

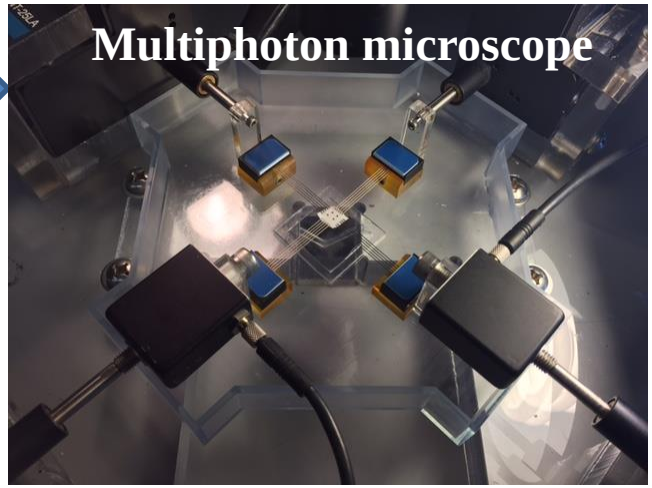
We used mechanical loading (biaxial stretching) and multi-photon microscopy- to examine collagen organization; re-alignment and recruitment



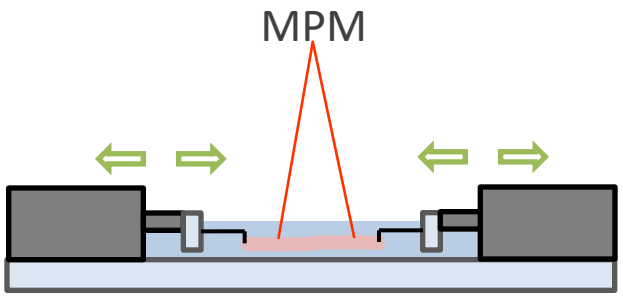




Markers used to calculate strain



Biaxial testing

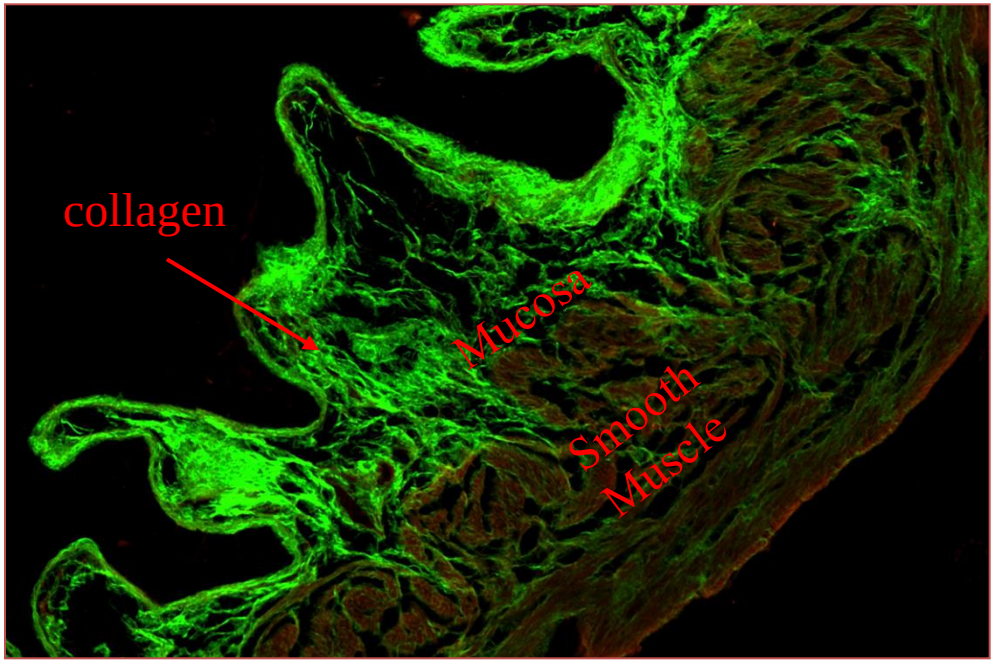


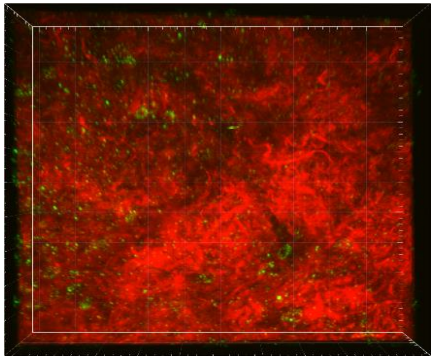
- Stretched at discrete increments
- Imaged at each stretch level

Overall goal- to examine how ECM components (collagen) contribute to *mechanical behavior of the bladder in aging*

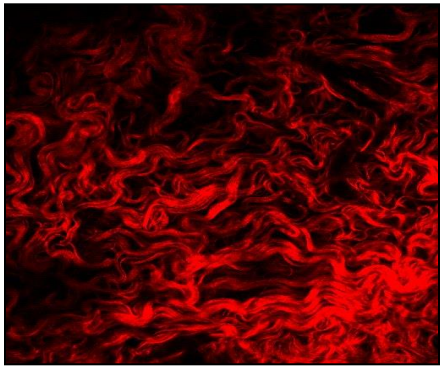
Collagen fibers are oriented differently through the bladder wall

ECM (collagen): mucosal fibers are more uniform versus SM fibers





Fine fibers- woven- wavy distribution (Mucosa)

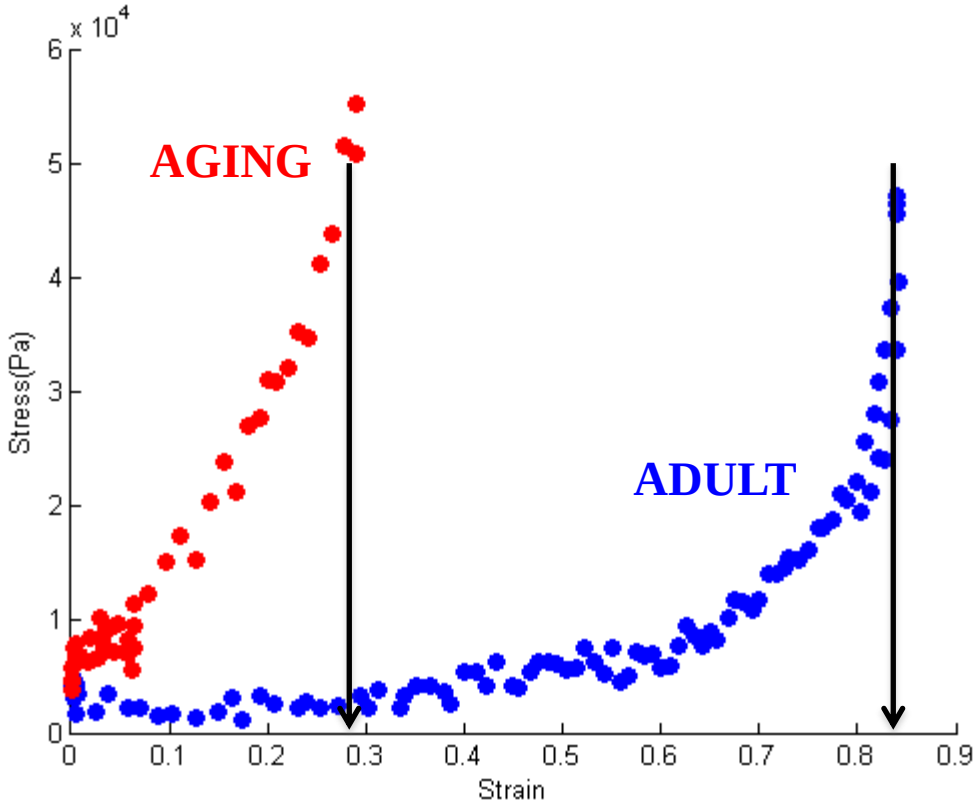


Large diameter fibers (smooth muscle)

Mucosal versus muscle ECM (collagen) fibers exhibit different responses to mechanical loading (stretch)

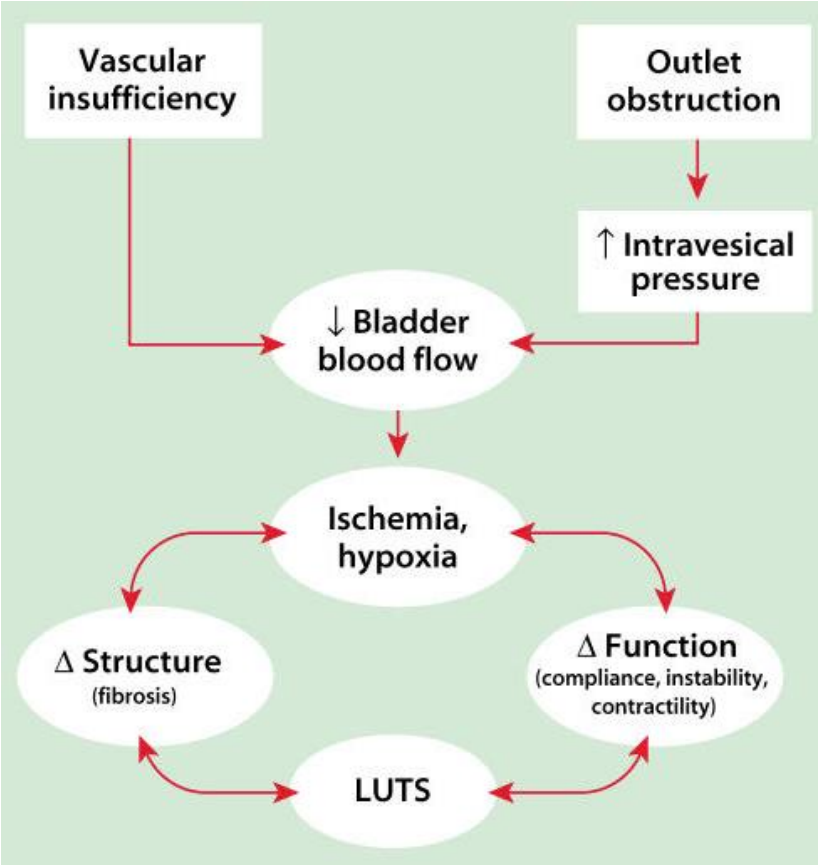
Stretch-induced collagen (orientation/recruitment) is altered in aging bladder

The ECM ‘stiffness’ can be modulated in disease and aging



Vascular changes (ischemia) often accompany the development of fibrosis

Lower Urinary Tract Symptoms *(instability, impaired contractility, changes in bladder volume and flow rate)*- can increase in frequency with age



Underlying mechanisms can include changes in blood flow and oxidative stress- this can impact neuronal and non-neuronal targets

Summary and Research Opportunities

- ✓ The ECM balances mechanical loads throughout the bladder wall *(involved in structural support ; cellular function)*.
- ✓ Differences in mucosal/SM collagen orientation/recruitment - suggest different roles in bladder health and disease.
- ✓ Aging alters *remodeling* of vasculature and ECM proteins (ECM fibers may break, thicken, stiffen, clump together and lose elasticity with increased stretch).
- ✓ Additional studies may lead to insights into biomechanical properties of the bladder wall and how sensory properties may be altered in aging.