

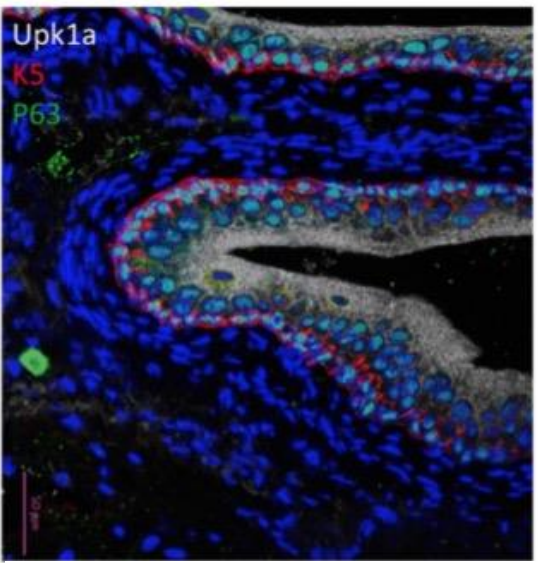
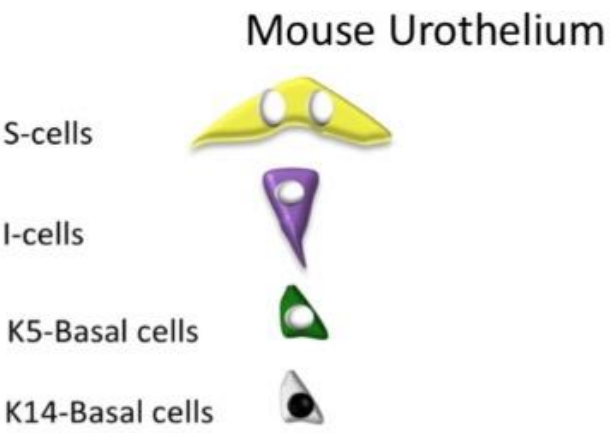
What does benign bladder research need?

Greg Whittemore, MD/MS Candidate, Class of 2023
Columbia University Vagelos College of Physicians & Surgeons
Research Assistant in Mendelsohn & Sanna-Cherchi Labs
Department of Urology and Division of Nephrology, Department of
Medicine, Columbia University Irving Medical Center



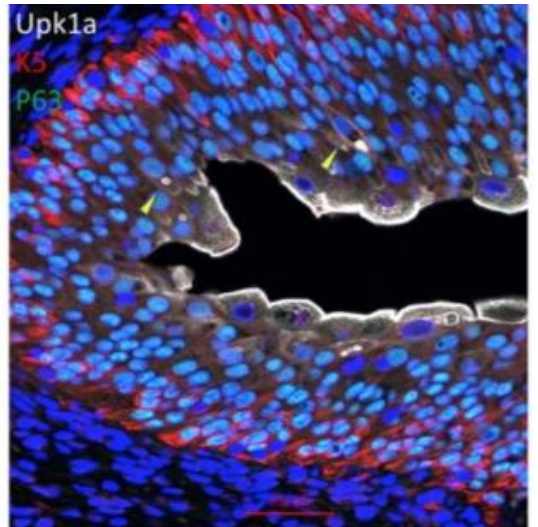
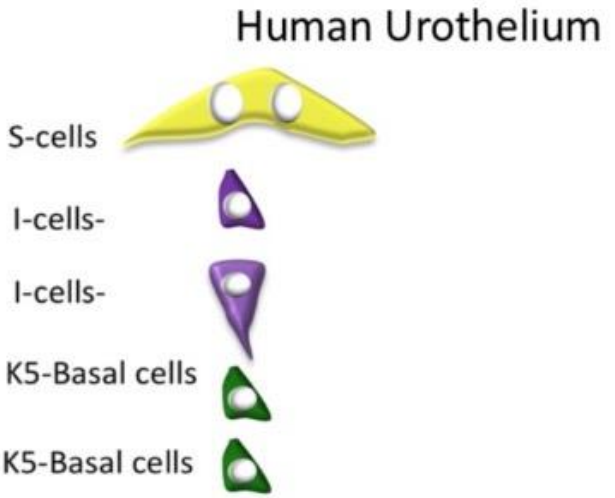
A brief tour of the urothelium

Krt20	Fabp4	Uchl1	Upk	Pparg	Shh	Krt5	Krt14	P63
Red	Red	Red	Red	Red	Green	Green	Green	Green
Green	Green	Green	Red	Red	Red	Green	Green	Red
Green	Green	Green	Green	Red	Red	Red	Green	Red
Green	Green	Green	Green	Red	Red	Red	Red	Red



Adult Mouse

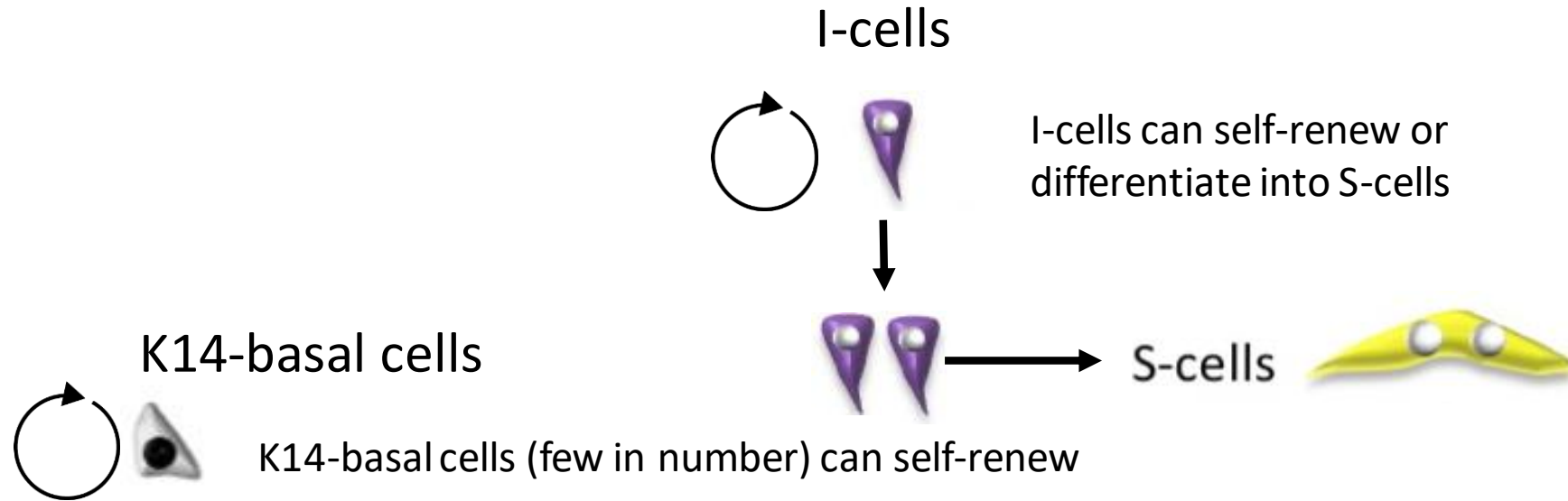
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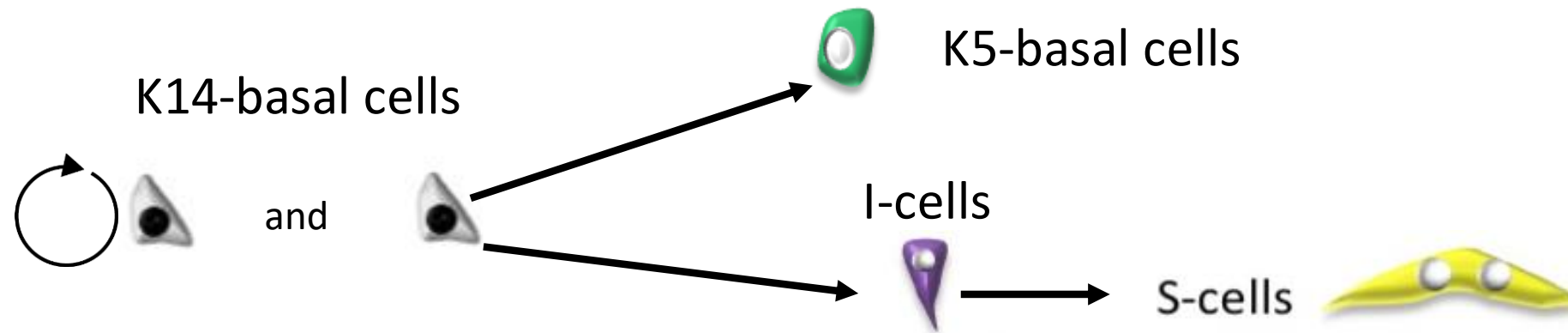
Adult Human

Different classes of urothelial progenitors

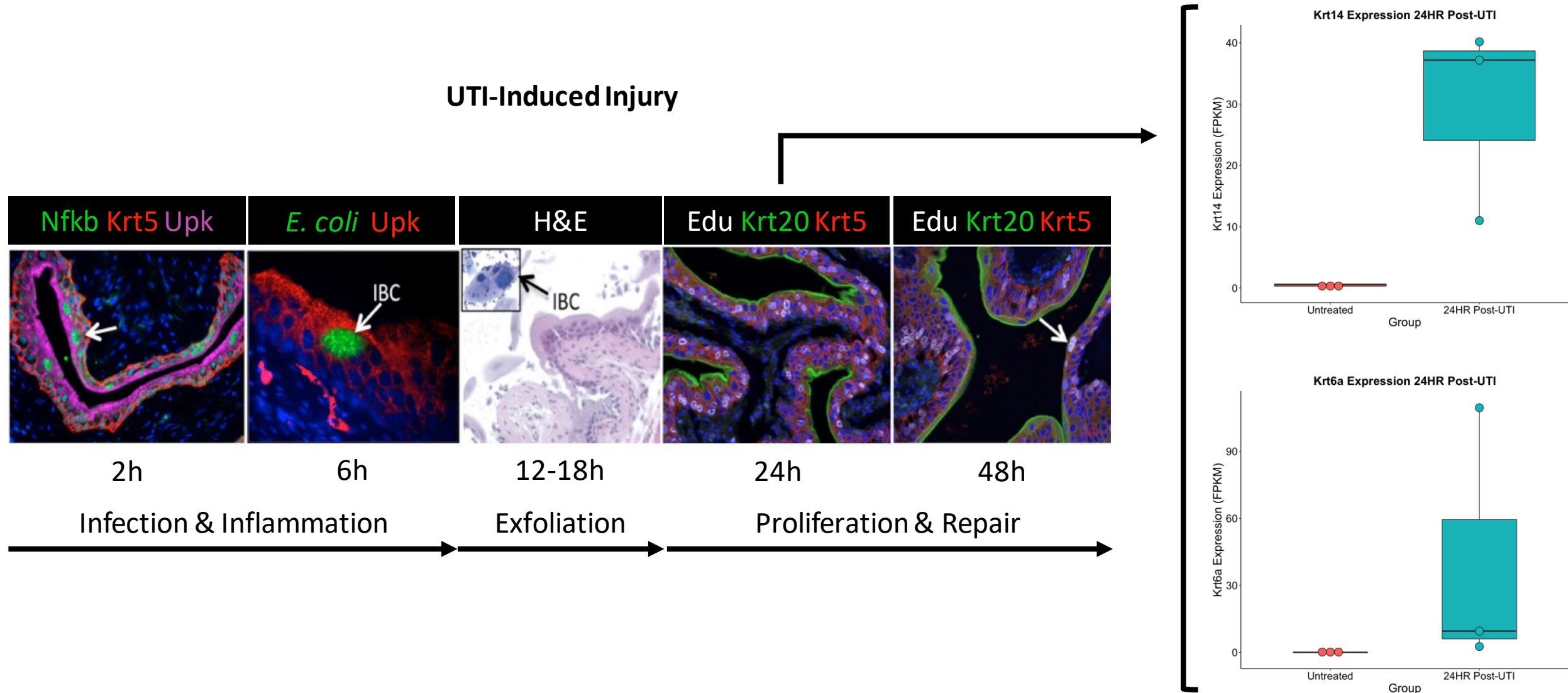
At homeostasis: I-cells are progenitors that differentiate into S-cells and repair urothelium after acute/minor injury



After chronic or serious injury: I-cells are depleted, K14-basal cells expand and regenerate the urothelium *de novo* (**RARE!**)



The urothelium is one of the most quiescent epithelia in the body, but can rapidly regenerate after injury



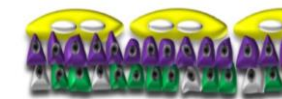
K14-basal progenitors acquire a transient "activated" state in response to injury

BBN=Transient injury/Carcinogenesis
CPP=Urothelial injury

BBN or 5xCPP



Normal urothelium



Luminal markers

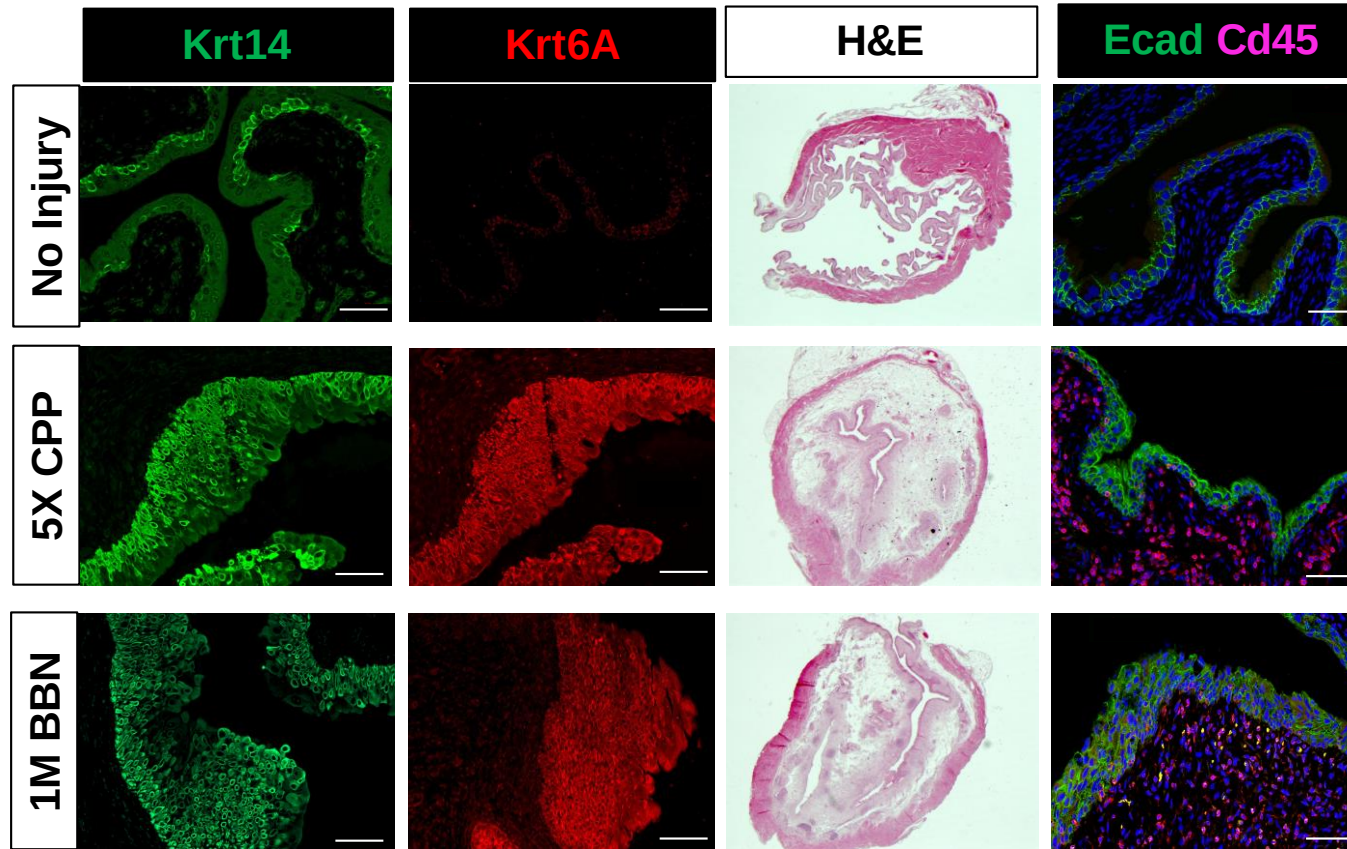
Krt20+
Krt18+
Gata3+
Pparg+

Activated urothelium



Basal markers

Krt14+
Krt6a+
Krt16+
Krt1+

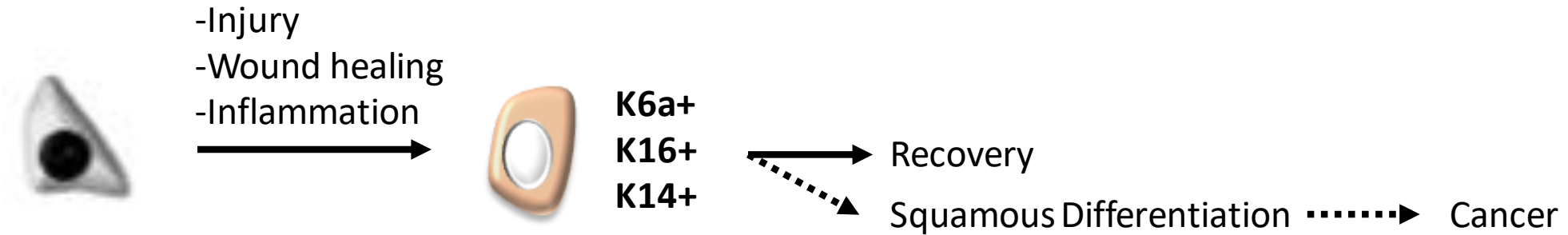


Activated basal cells form in response to injury and prime the urothelium for tumor formation

- Stereotyped injury response occurs in epithelial barriers (skin, airways, urothelium, etc) as a means of protection
- Occurs ***transiently*** in response to acute injury
- Response sustained in setting of chronic injury → squamous metaplasia

K14-Basal Progenitor

Activated Basal Cells





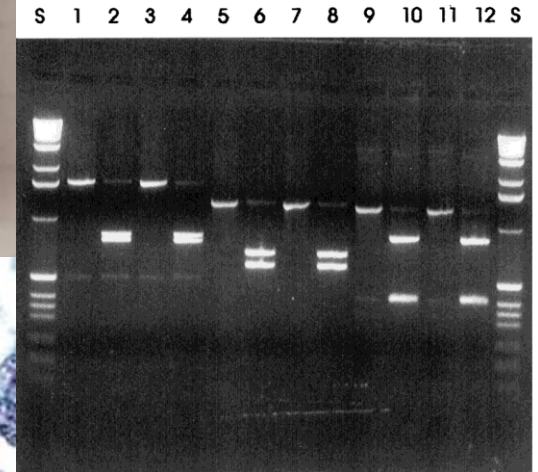
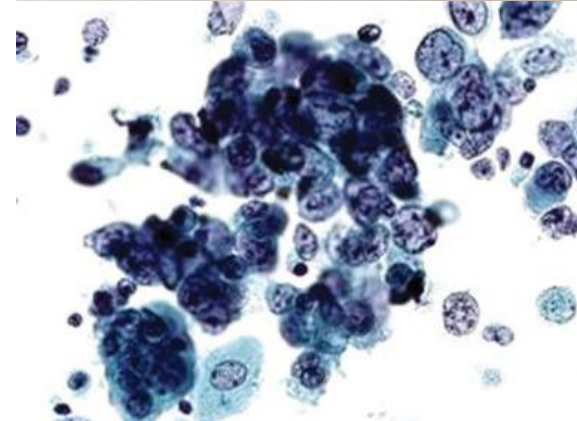
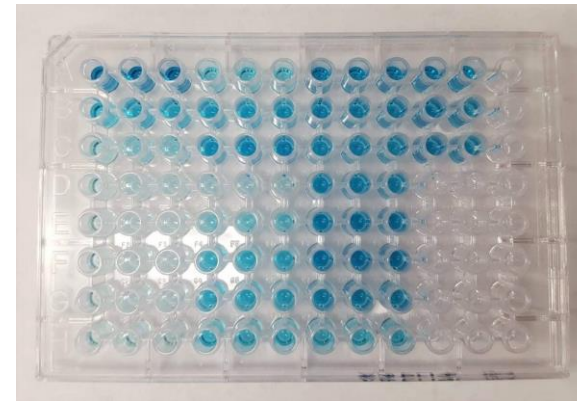
Is it getting hot in here?

Taking the temperature of the bladder

Can we use what we know from mouse models of urothelial damage and use KRT6A and KRT14 as urine biomarkers to assess disease state of the human urothelium?

Where might a test for urothelial damage help, and what would it look like?

- Red flag for urothelial injury
- May aid with diagnosis, management, prognostication of benign bladder disease
 - Lower Urinary Tract Dysfunction
 - Overactive Bladder
 - Nocturia
 - Neurogenic Bladder
 - Underactive Bladder
 - Diabetic Bladder Dysfunction
 - Lower Urinary Tract Symptoms
 - UTI
 - Iatrogenic or idiopathic urothelial damage
 - Interstitial Cystitis/Bladder Pain Syndrome
 - Mesh erosion, other post-operative complications
- Could help triage patients for imaging, cystoscopy





Does anybody have a map?

An argument for a genome atlas of benign bladder diseases

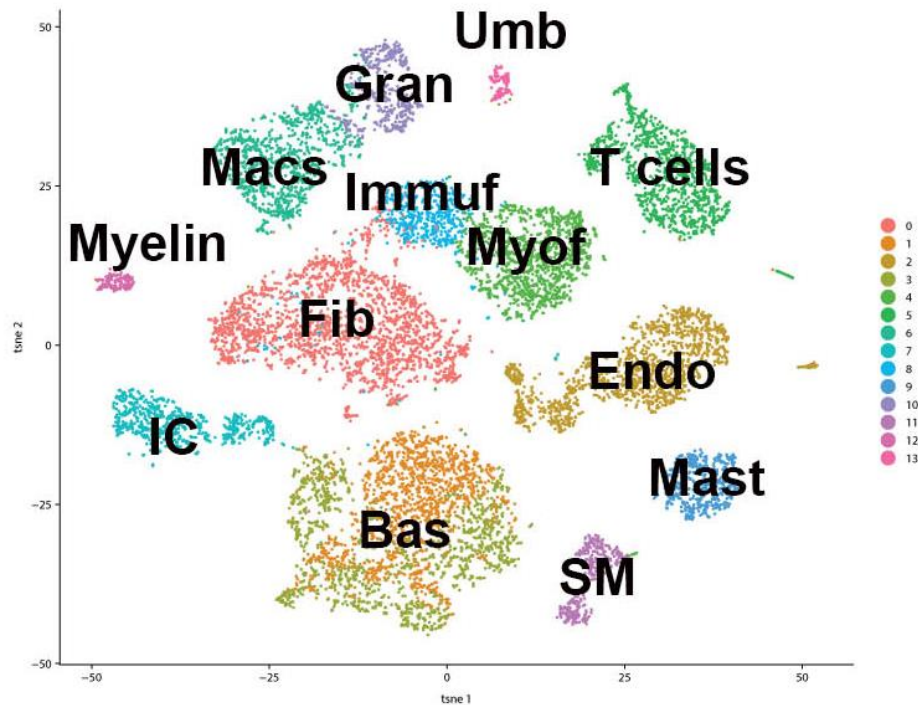
What do we serve to gain – learning from successes of The Cancer Genome Atlas

- Dissection of molecularly distinct subtypes of disease (sequencing and unsupervised clustering)
- Better characterize molecular pathophysiology
- Discovery of biomarkers for diagnosis, prognostication, and monitoring of treatment efficacy
- Improve therapy by identification of pathways for intervention with currently available agents and guiding novel drug discovery
- Identification of genetic risk factors
- May allow for developing preventative treatments for patients at risk

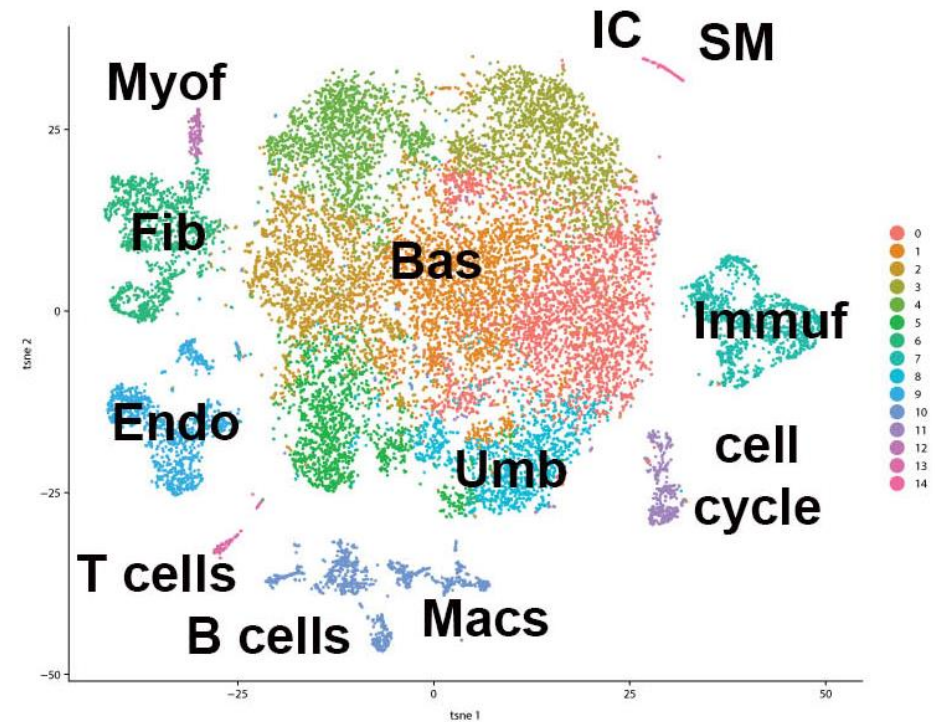
Where to start?

A single-cell atlas of the healthy adult bladder

HUMAN



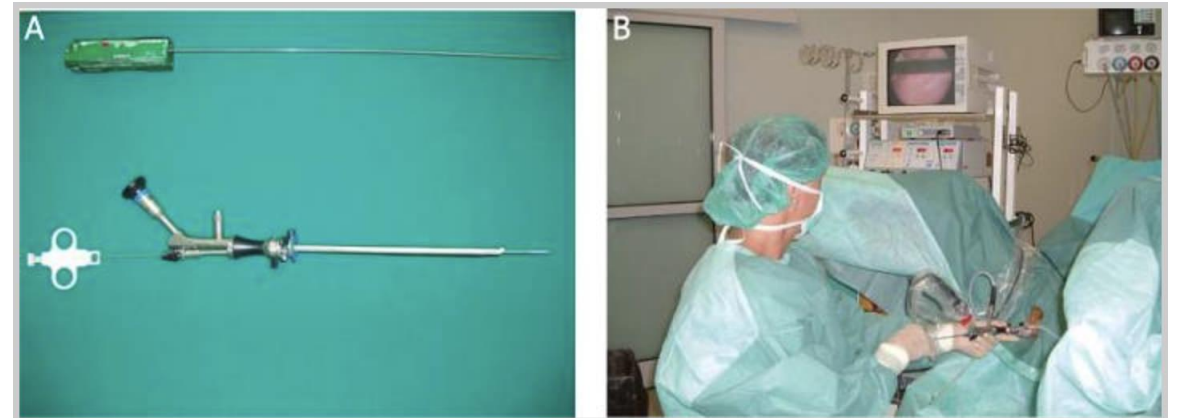
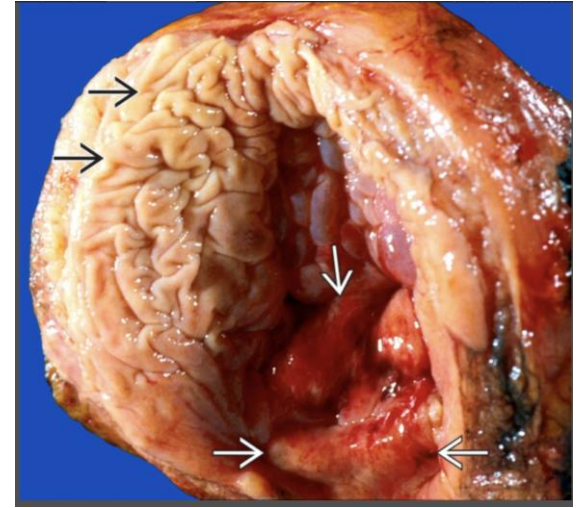
MOUSE



Unpublished data from Doug Strand

Strategies for tissue acquisition

- Post-mortem bladder recovery
- Bladder biopsy
- FFPE tissue (Doug Strand's Biobank!)
- Blood samples

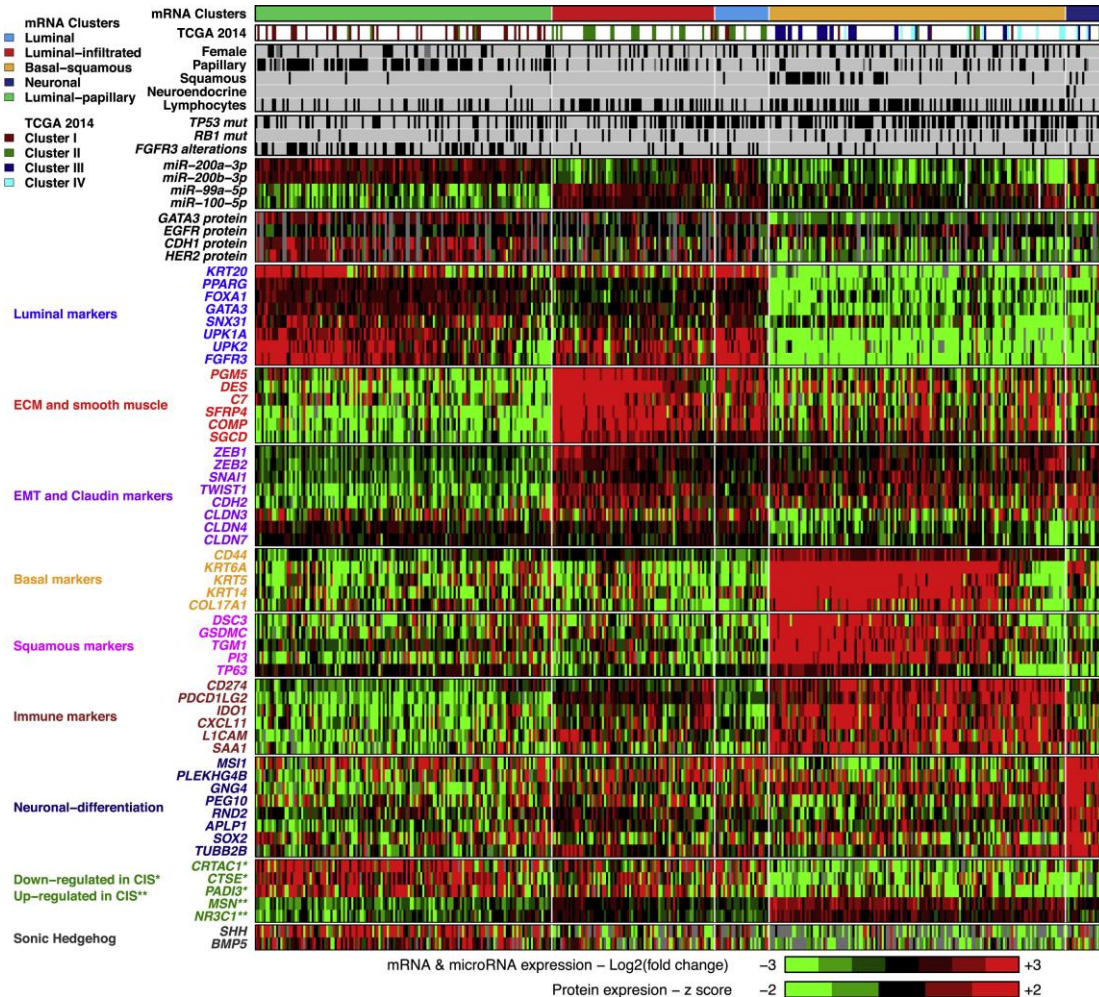


Top: Mitchell Tublin MD, et al. "Introduction to the Bladder" *Imaging in Urology*, 200-203. Elsevier 2018

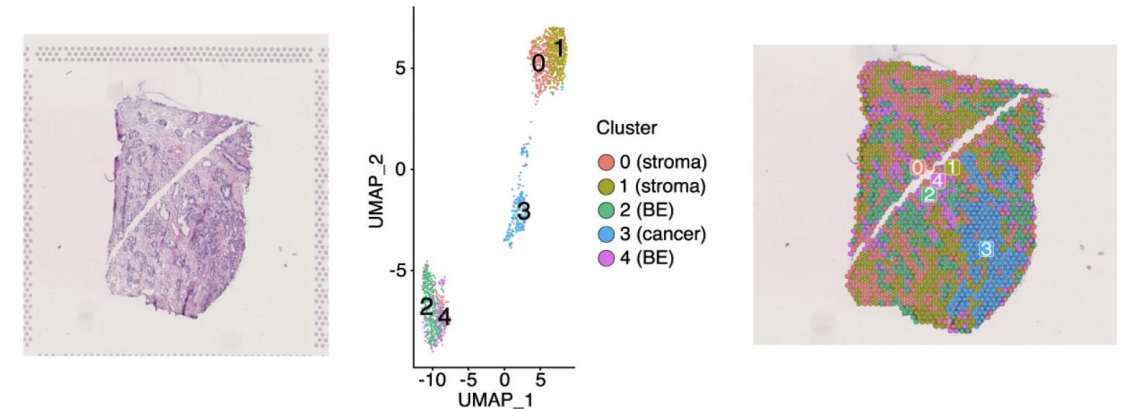
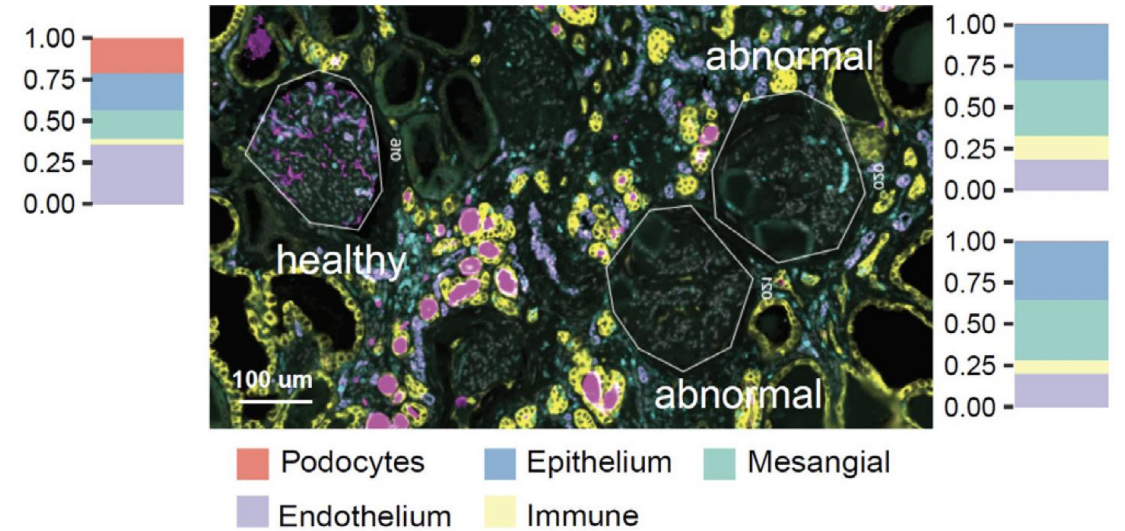
Bottom: Chlosta et al. *Arch Med Sci*, 2010. PMID: 22371776

So we have tissue...now what?

Sequencing and unsupervised clustering



Spatial transcriptomics



Robertson, A.G., et al. *Cell*, 2017. PMID: 28988769

<https://www.illumina.com/content/dam/illumina/gcs/assembled-assets/marketing-literature/ilmn-nanostring-geomx-app-note-m-gl-00223/ilmn-nanostring-geomx-app-note-m-gl-00223.pdf>

Taavitsainen, S., et al. *Nature Communications*, 2021. PMID: 34489465

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