Hvordan forskning i grise kan fremskynde nye behandlinger mod UVI

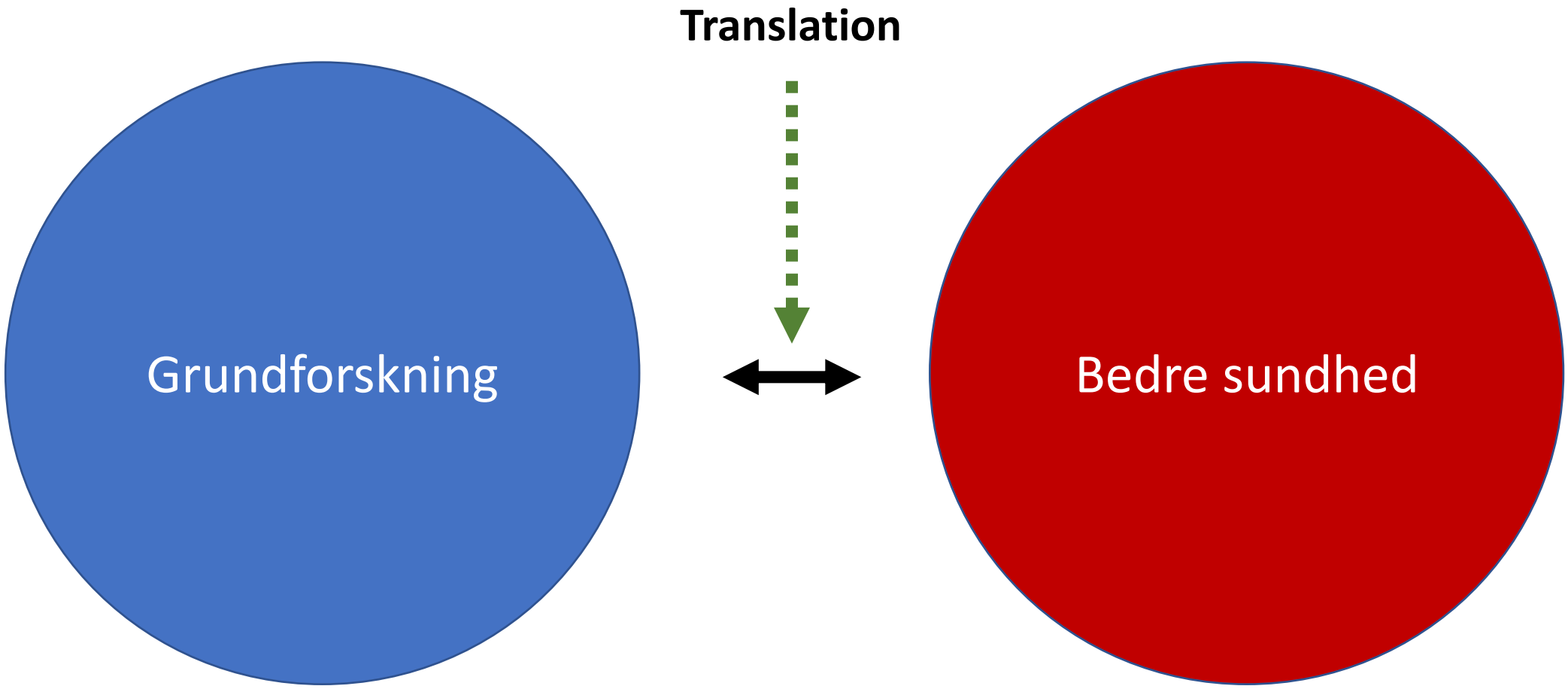
FSUIS landskursus

Kristian Stærk, læge, Phd

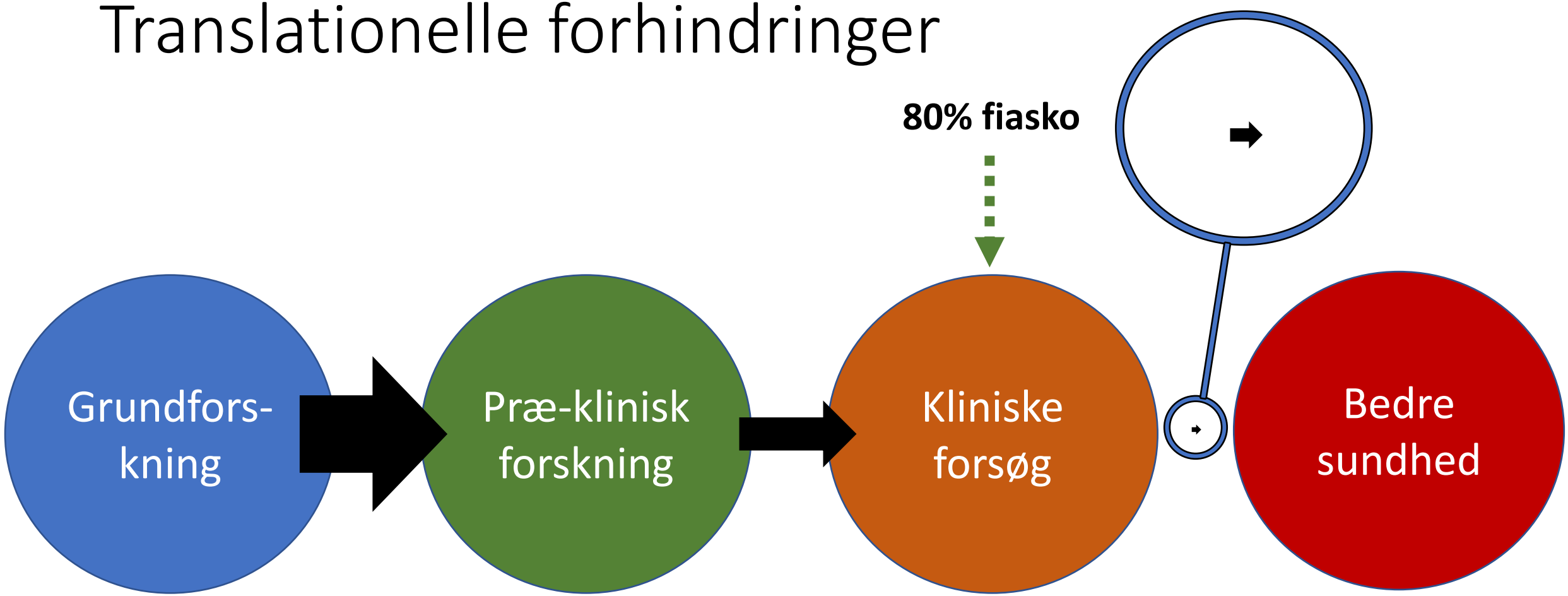
Klinisk Mikrobiologisk afdeling, OUH

20.09.2022

Translationel forskning



Translationelle forhindringer



Præ-kliniske modeller for UVI = mus!

Præ-klinisk forskning

NATURE | NEWS

Misleading mouse studies waste medical resources

Retrospective of more than 100 failed drugs show many should have never made it to clinical trials.

Erika Check Hayden

26 March 2014

PNAS

Genomic responses in mouse models poorly mimic human inflammatory diseases

Junhee Seok[a,1], H. Shaw Warren[b,1], Alex G. Cuenca[c,1], Michael N. Mindrinos[a], Henry V. Baker[c], Weihong Xu[a], Daniel R. Richards[d], Grace P. McDonald-Smith[e], Hong Gao[a], Laura Hennessy[f], Celeste C. Finnerty[g], Cecilia M. López[c], Shari Honari[f], Ernest E. Moore[h], Joseph P. Minei[i], Joseph Cuschieri[j], Paul E. Bankey[k], Jeffrey L. Johnson[h], Jason Sperry[l], Avery B. Nathens[m], Timothy R. Billiar[l], Michael A. West[n], Marc G. Jeschke[o], Matthew B. Klein[j], Richard L. Gamelli[p], Nicole S. Gibran[j], Bernard H. Brownstein[q], Carol Miller-Graziano[k], Steve E. Calvano[r], Philip H. Mason[e], J. Perren Cobb[s], Laurence G. Rahme[t], Stephen F. Lowry[r,2], Ronald V. Maier[j], Lyle L. Moldawer[c], David N. Herndon[g], Ronald W. Davis[a,3], Wenzhong Xiao[a,t,3], Ronald G. Tompkins[t,3], and the Inflammation and Host Response to Injury, Large Scale Collaborative Research Program[4]

[a]Stanford Genome Technology Center, Stanford University, Palo Alto, CA 94305; Departments of [b]Pediatrics and Medicine, [s]Anesthesiology and Critical Care Medicine, and [l]Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114; [c]Department of Surgery, University of Florida College of Medicine, Gainesville, FL 32610; [d]Ingenuity Inc., Redwood City, CA 94063; [e]Department of Surgery, Massachusetts General Hospital, Boston, MA 02114; [f]Department of Surgery, Harborview Medical Center, Seattle, WA 98195; [g]Shriners Hospitals for Children and Department of Surgery, University of Texas Medical Branch, Galveston, TX 77550-1220; [h]Department of Surgery, University of Colorado Anschutz Medical Campus, Denver, CO 80045; [i]Department of Surgery, Parkland Memorial Hospital, University of Texas, Southwestern Medical Center, Dallas, TX 75390; [j]Department of Surgery, Harborview Medical Center, University of Washington School of Medicine, Seattle, WA 98195; [k]Department of Surgery, University of Rochester School of Medicine, Rochester, NY

Make mouse studies work

More investment to characterize animal models can boost the ability of preclinical work to predict drug effects in humans, says **Steve Perrin**.

Mice take the blame for one of the most uncomfortable truths in translational research. Even after animal studies suggest that a treatment will be safe and effective, more than 80% of potential therapeutics fail when tested in people. Animal models of disease are frequently condemned as poor predictors of whether an experimental drug can become an effective treatment. Often,

require patients to commit to year or more of treatment, during which they are precluded from pursuing other experimental options. Launching a clinical trial without the backing of robust animal data keeps patients out of tests for therapies that may have a better chance of success.

One such group of patients is those

ITIONS BY CLAIRE WELSH/*NATURE*

THE JOURNAL OF IMMUNOLOGY

BRIEF REVIEWS

Of Mice and Not Men: Differences between Mouse and Human Immunology

Javier Mestas and Christopher C. W. Hughes[1]

Mice are the experimental tool of choice for the majority of immunologists and the study of their immune responses has yielded tremendous insight into the workings of the human immune system. However, as 65 million years of evolution might suggest, there are significant differences. Here we outline known discrepancies in both innate and

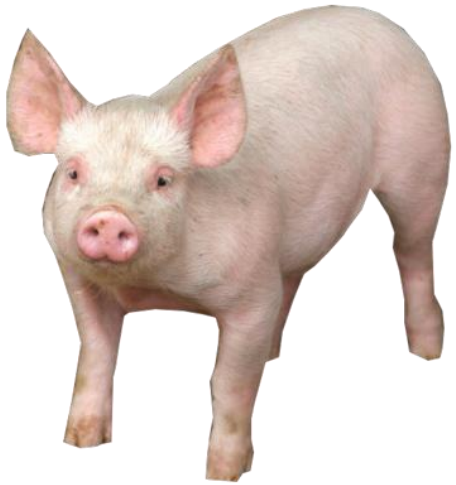
sarily true in humans. By making such assumptions we run the risk of overlooking aspects of human immunology that do not occur, or cannot be modeled, in mice. Included in this subset will be differences that may preclude a successful preclinical trial in mice becoming a successful clinical trial in human.

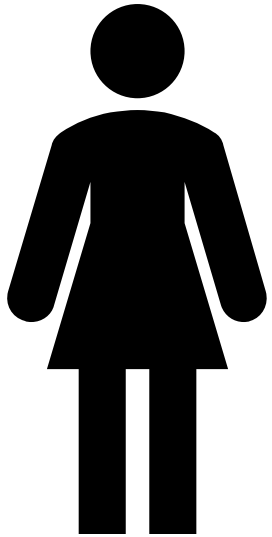
In this review our aim is not to suggest that the mouse is an

Formål

En intermediær model:

mere ”menneske-lignende”





Hvorfor grise?

I mere end 30 år har man anvendt grise-hjerteklapper i transplanationer

NEWS | 14 January 2022

First pig-to-human heart transplant: what can scientists learn?

Researchers hope that a person who has so far lived for a week with a genetically modified pig heart will provide a trove of data on the possibilities of xenotransplantation.

Sara Reardon

Genetically modified pig kidneys transplanted into a brain-dead person

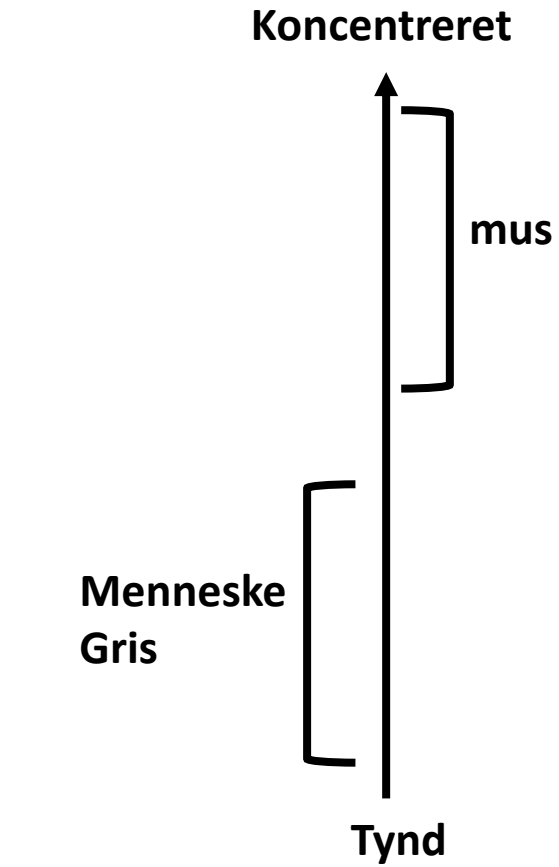
In an experiment paving the way for clinical trials, two pig kidneys produced urine for 77 hours after transplantation into the body of a man who was brain dead

HEALTH 20 January 2022

By Michael Le Page

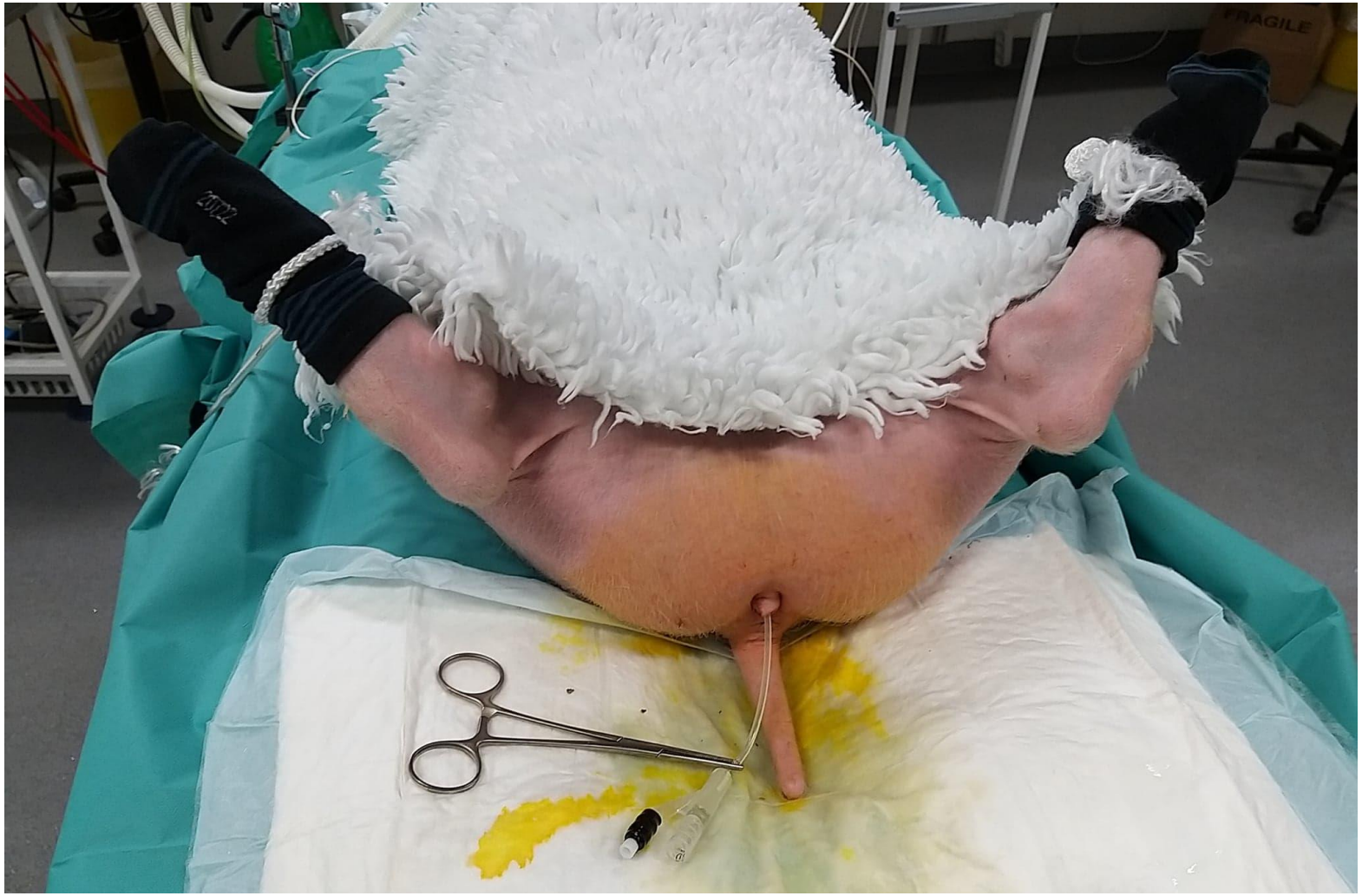
Ligheder mellem menneske og gris

- Anatomi og størrelse
- Fysiologi
- Urin
  - Produktion, massefylde, sammensætning
- Tarm mikrobiom
  - Grise er naturlige værter for humane uropatogener
- UVI er almindeligt i grise



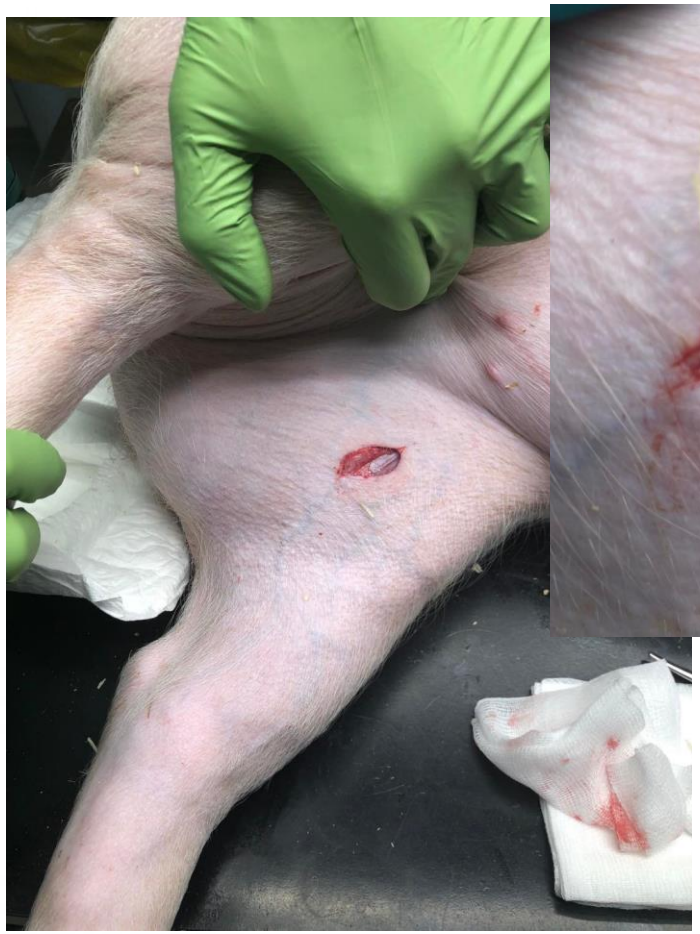
Model

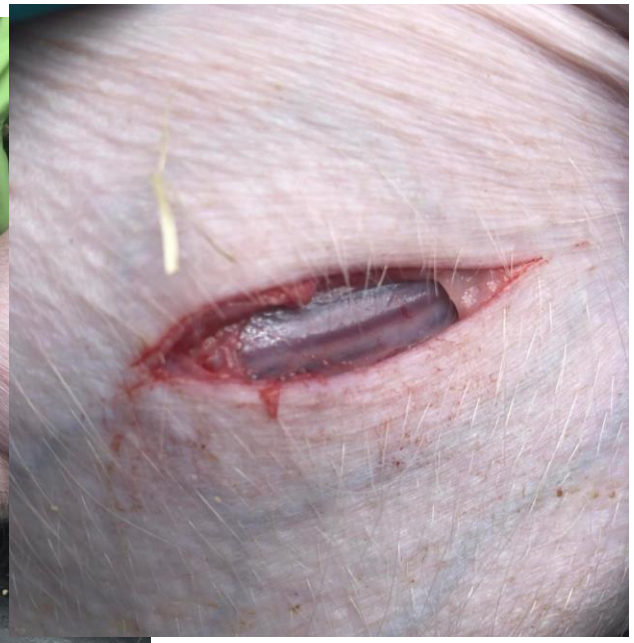
Inokulation



Urin

Blod



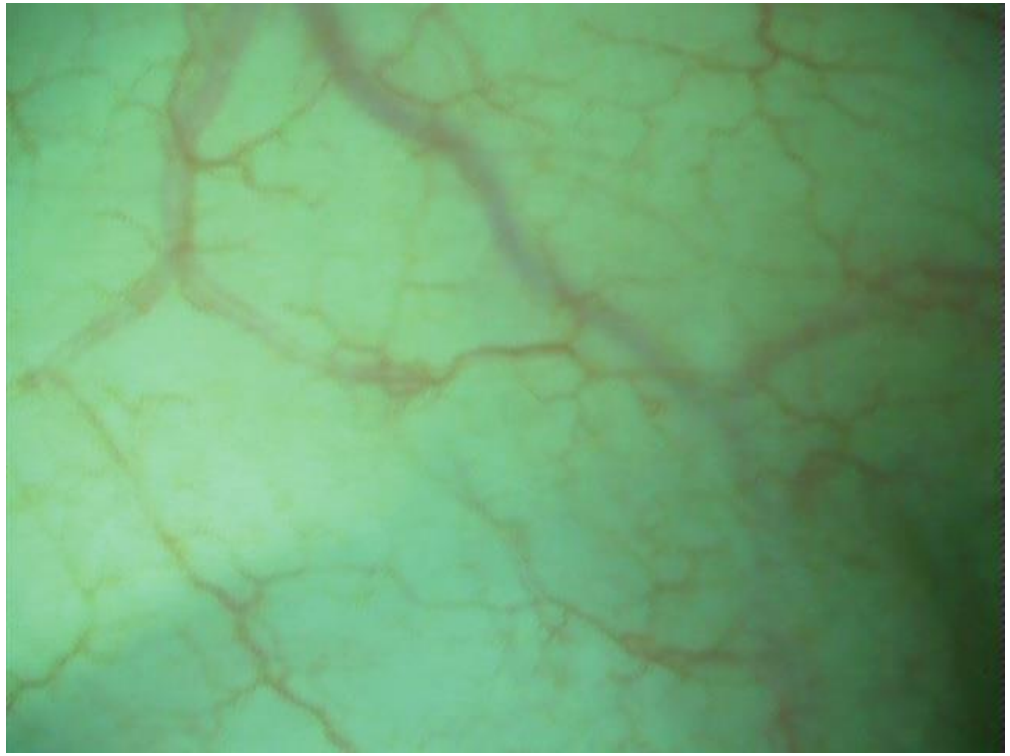


- Hvide blodceller
- CRP
- Antistoffer
- Neutralisationsforsøg

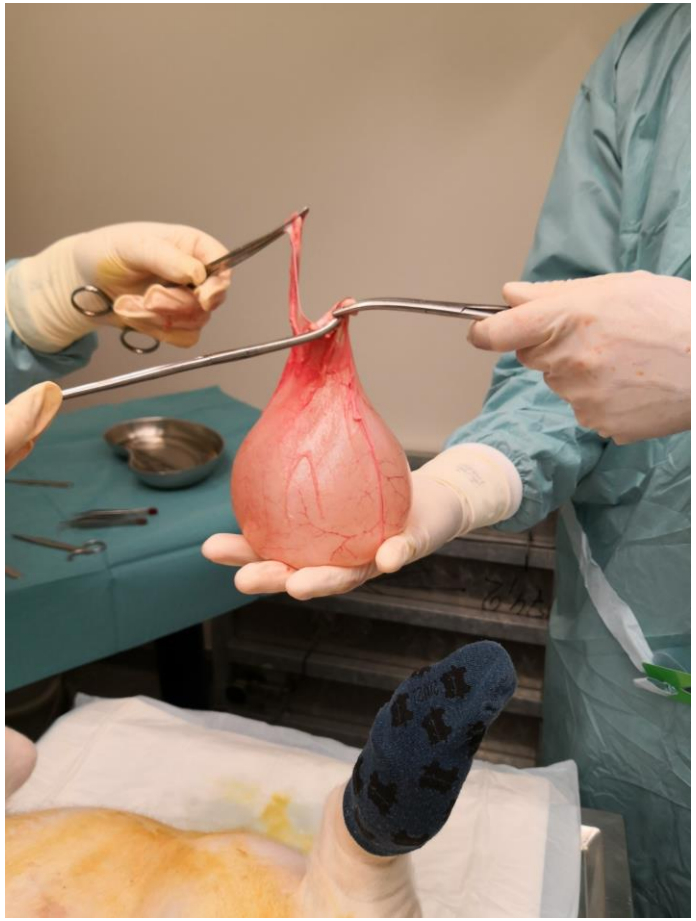
A. femoralis:
Op til 300 mL

Monitorering af infektion

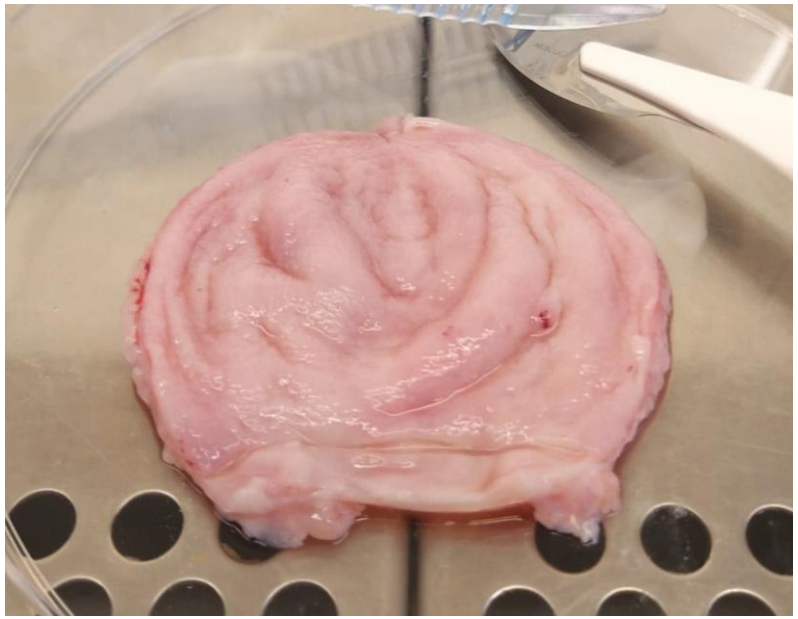
Cystoscopi



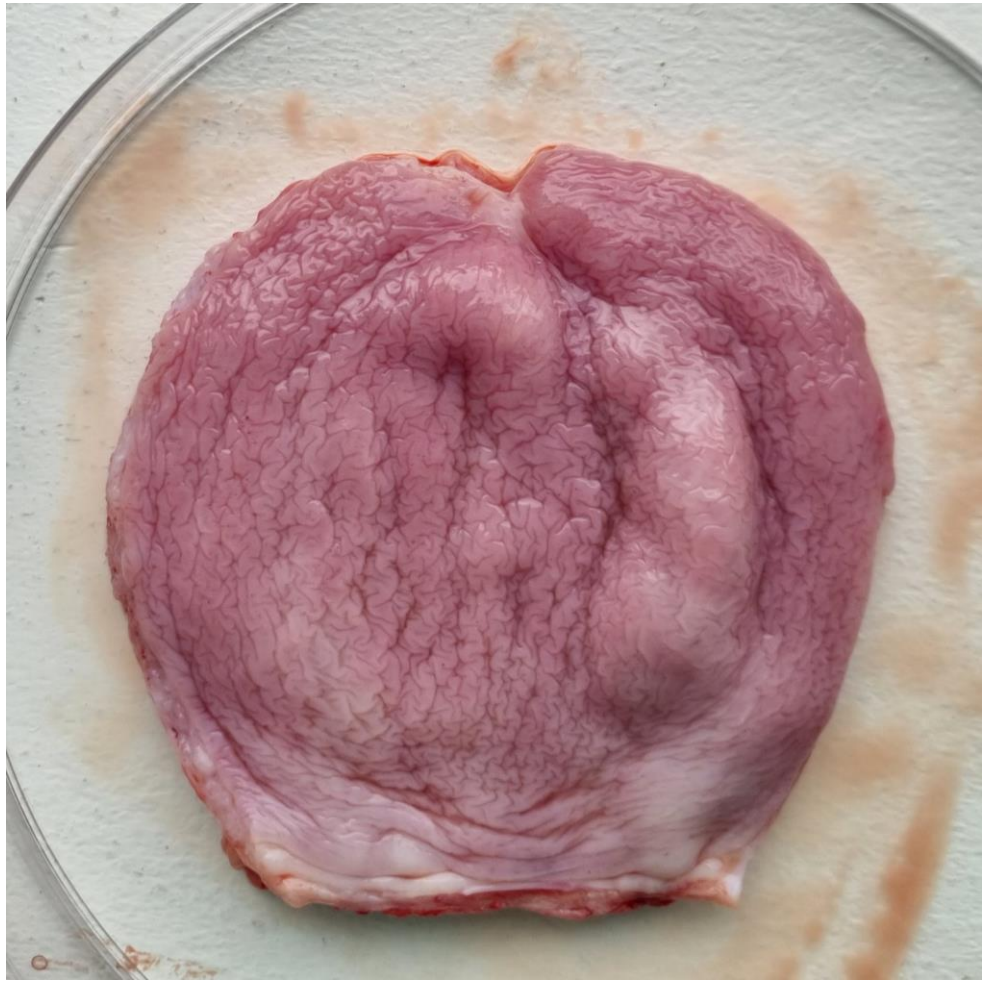
Aflivning



Blære

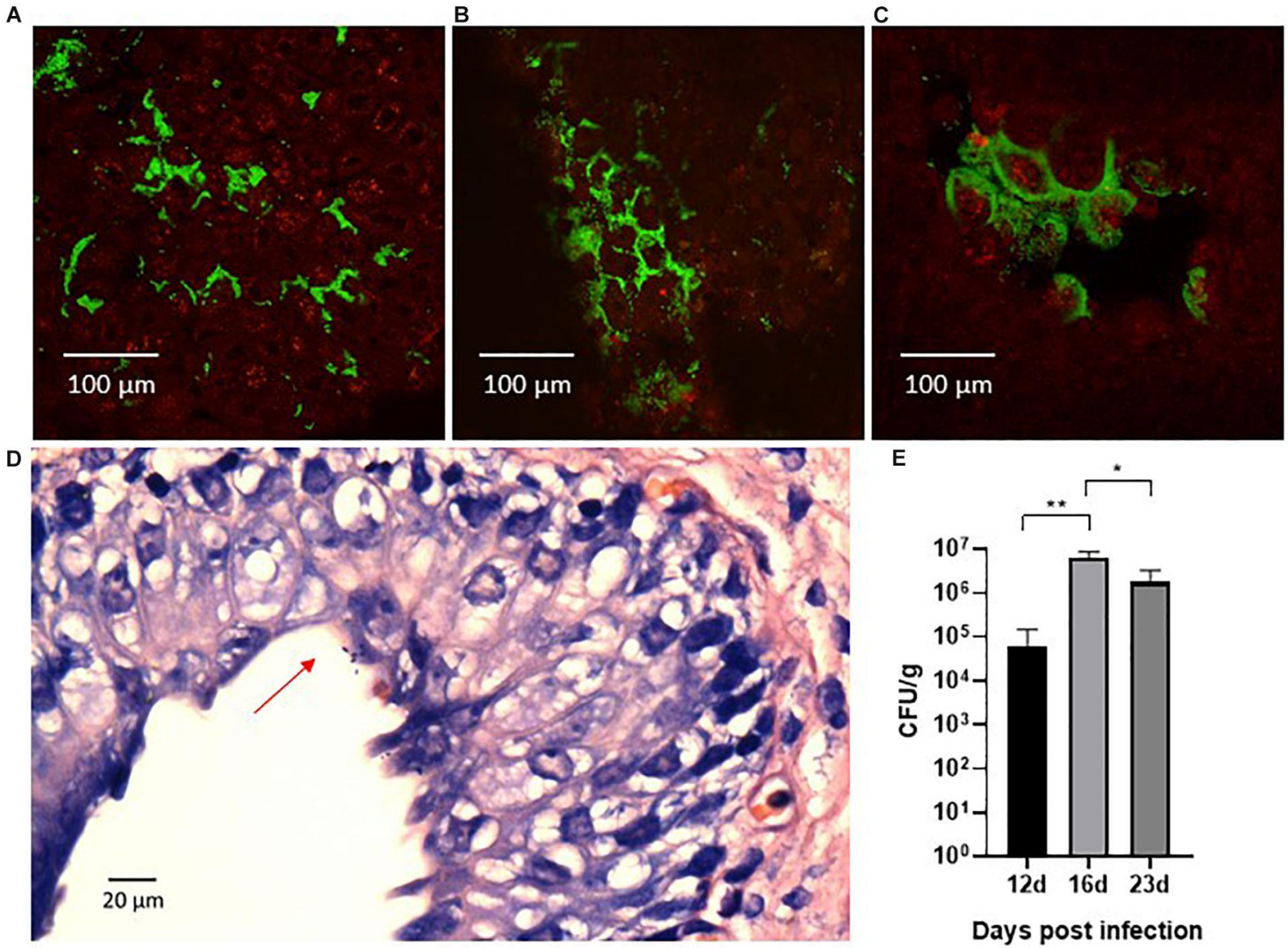


Nyre



Kontrol

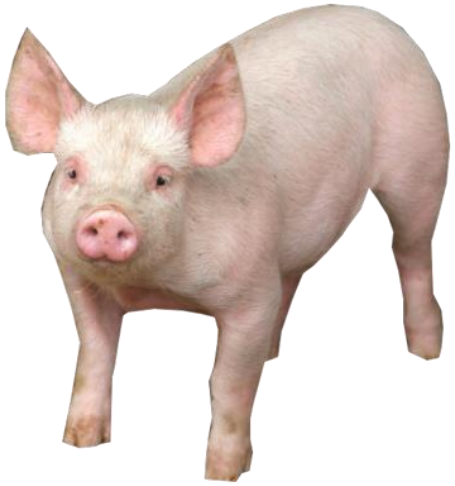
Inficeret


A
B
C
100 µm
100 µm
100 µm
D
20 µm
E
**
*
10^7
10^6
10^5
10^4
10^3
10^2
10^1
10^0
CFU/g
12d
16d
23d
Days post infection

Resultater og nuværende studier

UVI følsomhed

UVI følsomhed



100

100.000.000

Bakterier pr ml

Følsomhed – Hvorfor er det vigtigt?

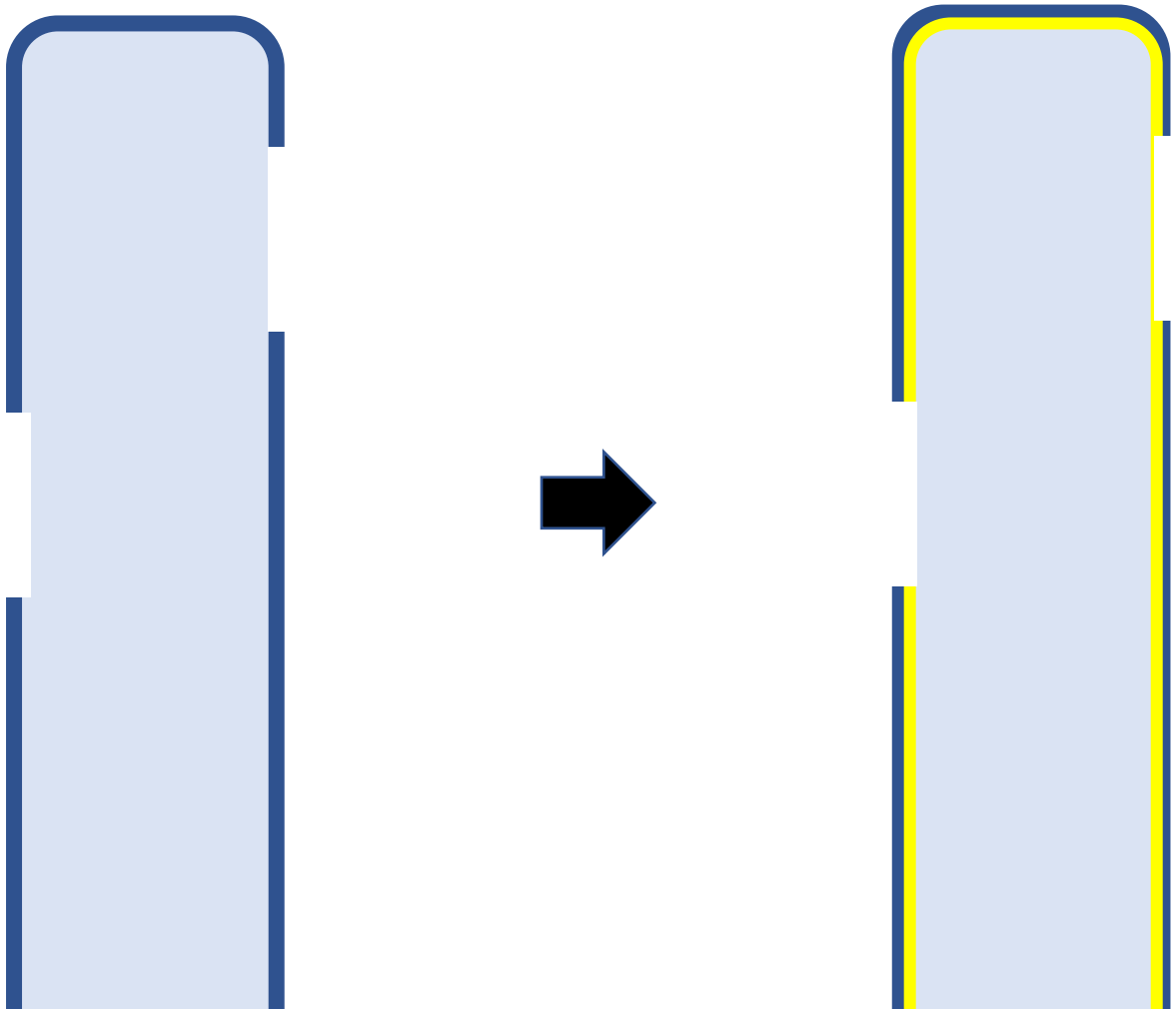
Afspejler følsomheden i mennesker

Tidlig kolonisation er en kritisk flaskehals

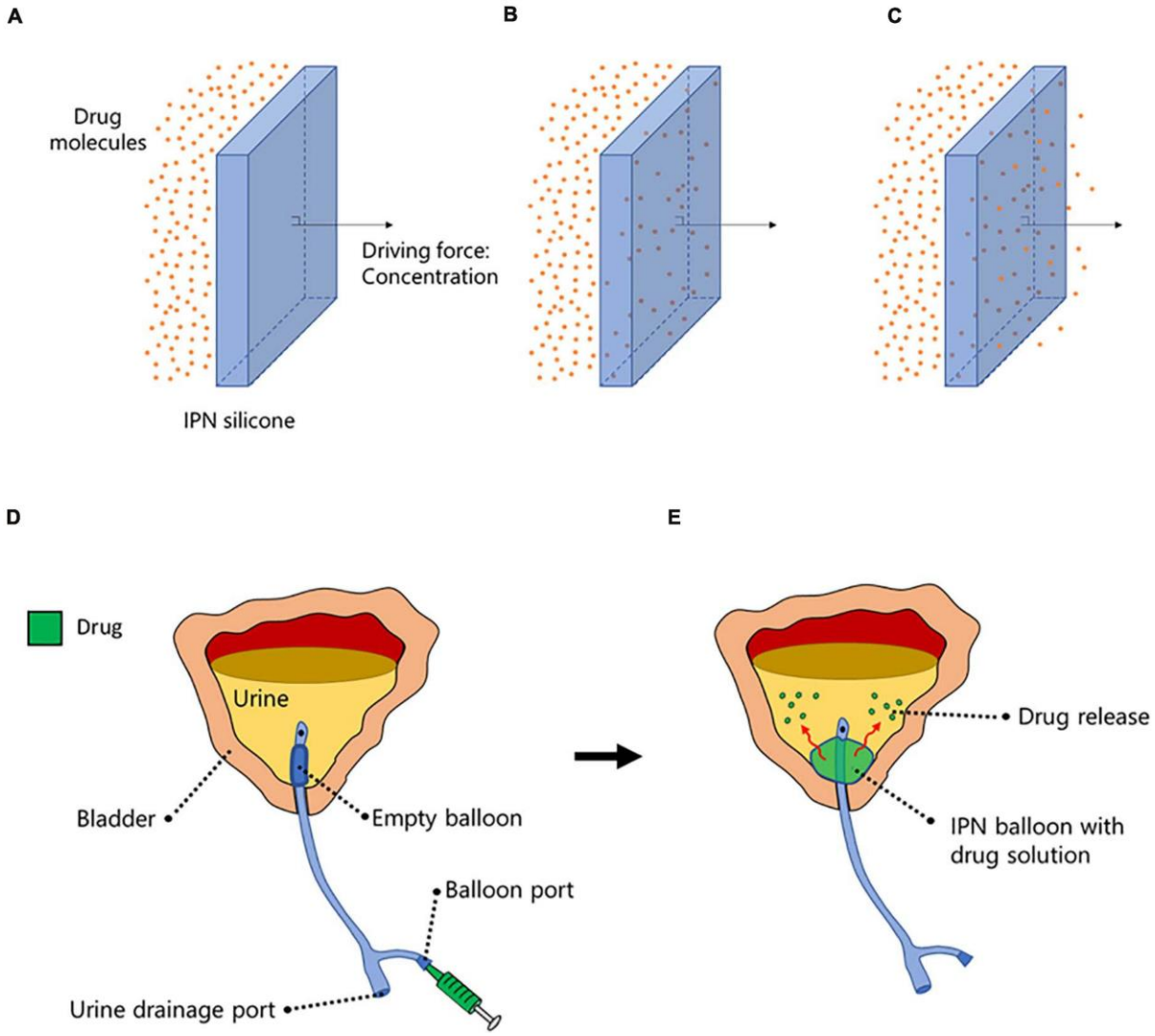
Overdreven inokulation kan tilsidesætte en terapeutisk effekt

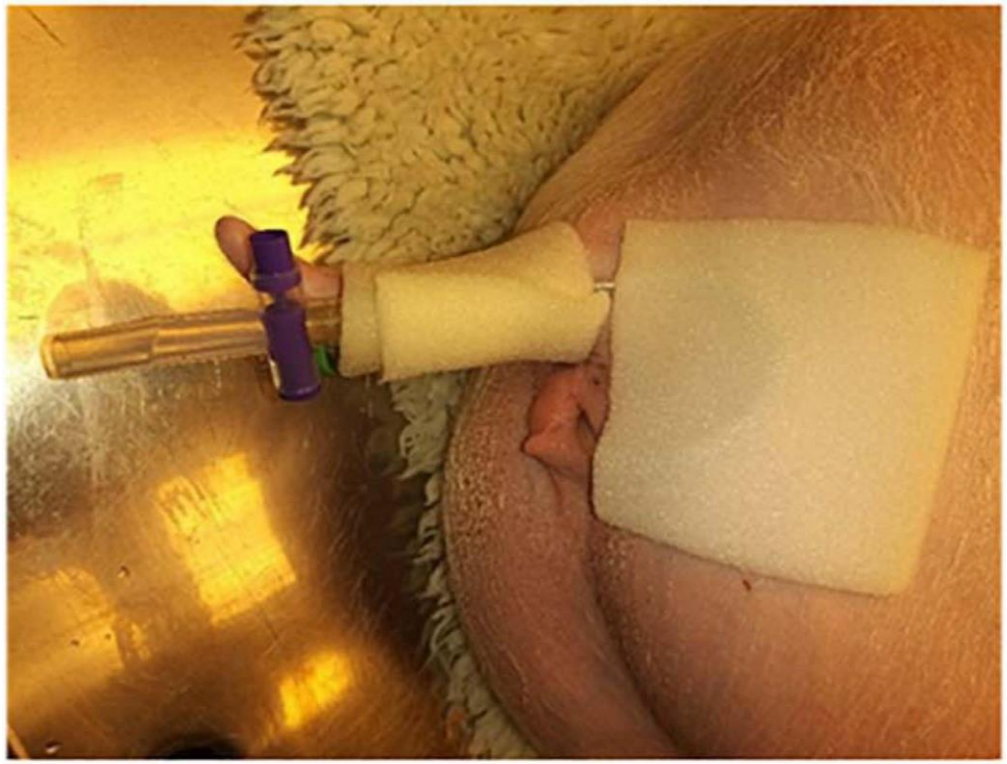
Antimikrobielle blærekatetre

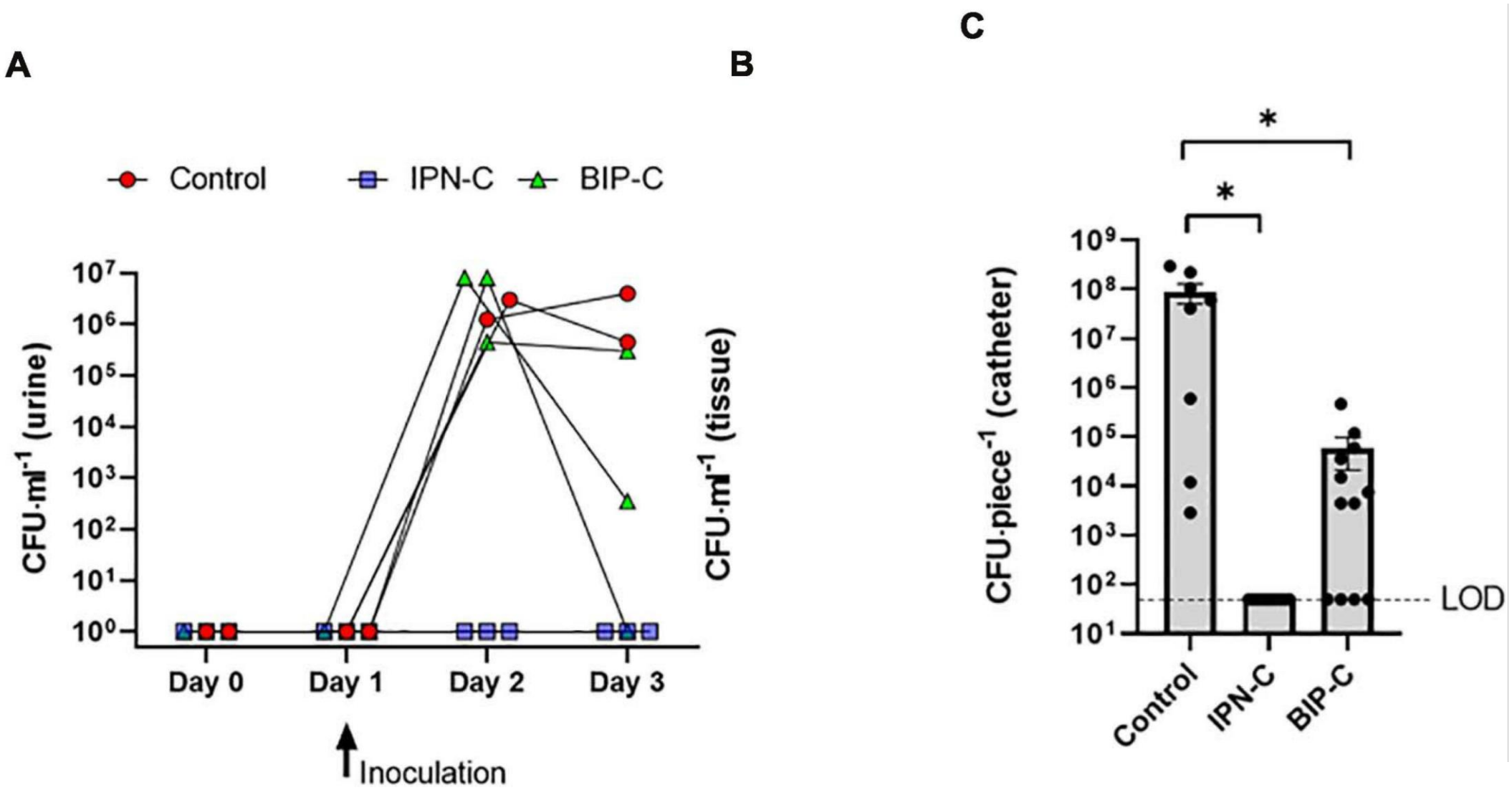
Klassisk coating koncept



Antimikrobielt blærekateter






A
B
C
Control
IPN-C
BIP-C
CFU·ml-1 (urine)
CFU·ml-1 (tissue)
Day 0
Day 1
Day 2
Day 3
Inoculation
CFU·piece-1 (catheter)
LOD
*
*

Fordele ved IPN-kateter

Antimikrobielle stoffer bypasser tarmen

- Resistens
- Bivirkninger

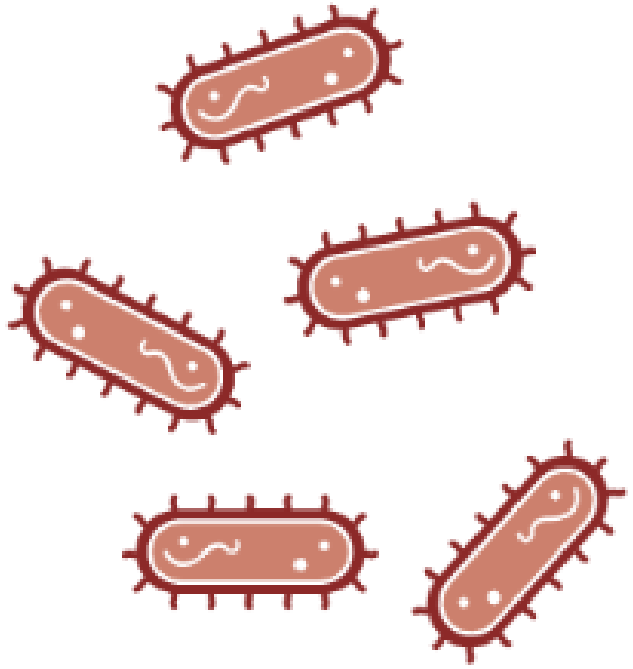
Konstant frigivelse af lægemiddel (ingen piller)

Bakteriel interferens

Niche besættelse

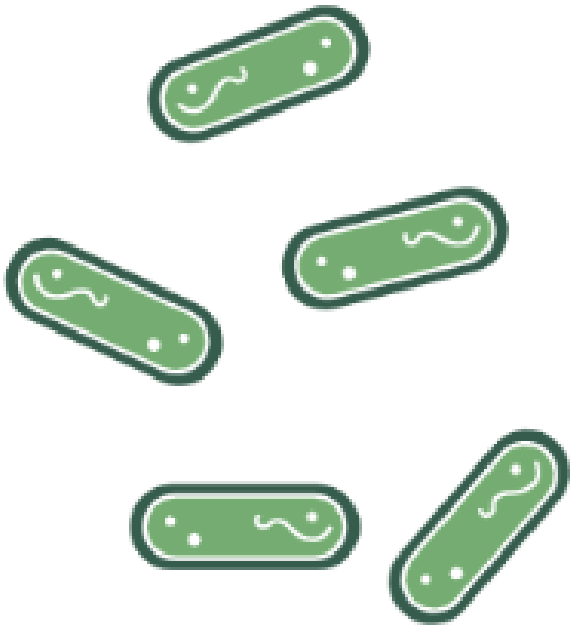
- Næring
- Plads
- Produktion af antimikrobielle stoffer

Symptomatiske *E. coli*



- Aktiverer immunsystemet
- Producerer virulensfaktorer (væksthæmning)
- Gror hurtigt i urin

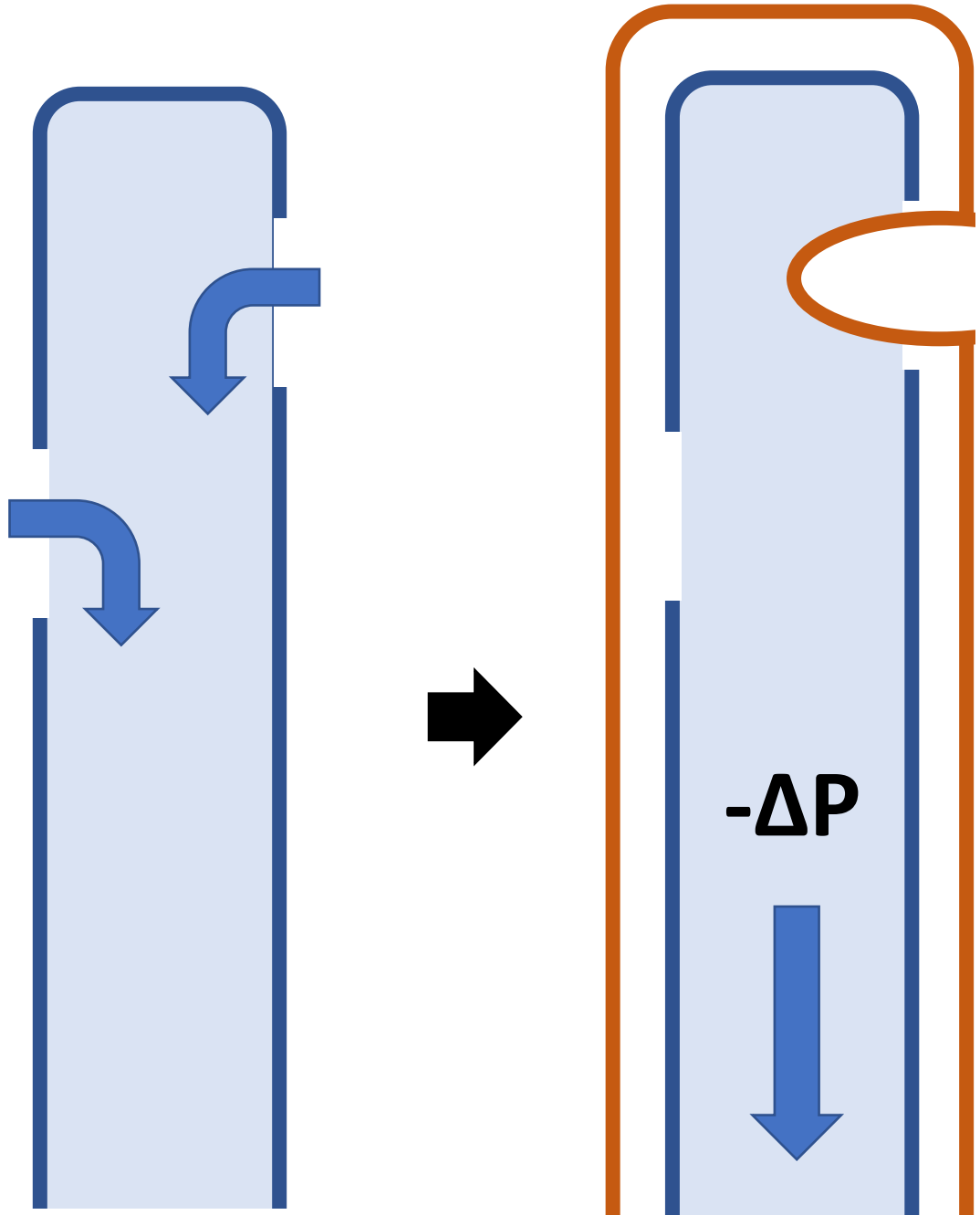
Asymptomatiske *E. coli*



- Usynlig for immunsystemet
- Gror meget hurtigt i urin

- Phd studie: Karin Andersen, urinvejskirurgisk afdeling, OUH
- Præ-klinisk griseforsøg
- Klinisk studie
- Resultater indtil videre

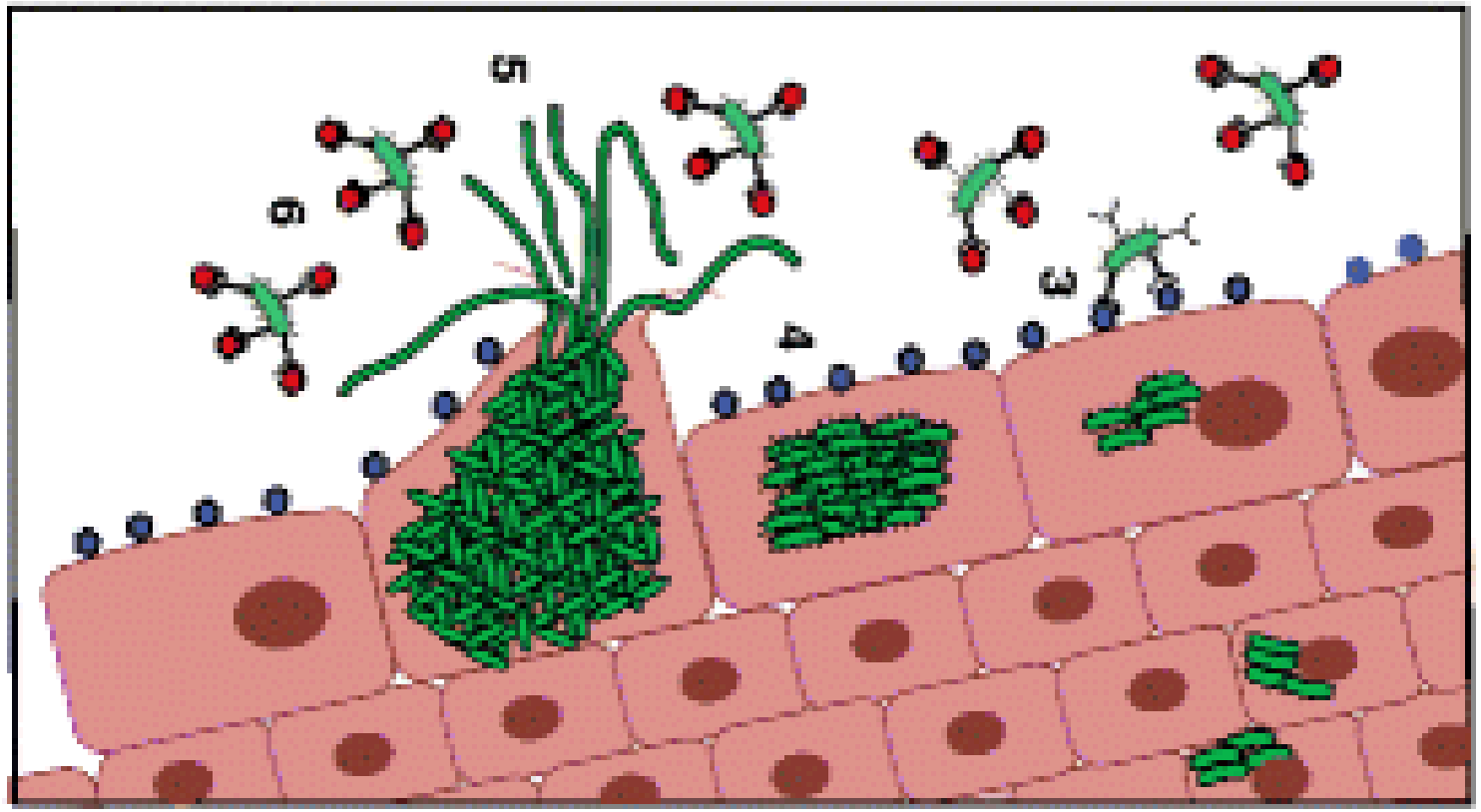
Kateter-associeret mikro-traumer: mulig årsag til UVI?


-ΔP

Gentagende UVI

Intracellulære blære-reservoir

- Recidiverende UVI/gentagende UVI
- Kronisk UVI
- Embedded UTI



Vaccination mod UVI

- Stor interesse
- Effekt
- Kost-effektive (grise)
- Stafylokokvaccine

Limitations

Dyrt

Understøtter ikke ”high-throughput studies” (selv hvis man havde pengene).

Konventionelle grise vokser hurtigt

Kræver særlige faciliteter og personale

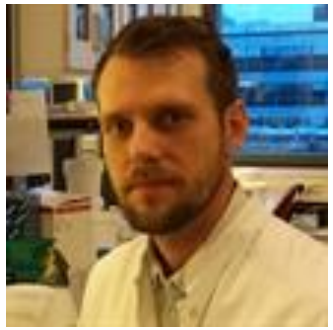
Den molekylære værktøjskasse er lille og der er få gen-modificerede racer

Konklusion

- Grisen rekapitulere vigtigt aspekter af UVI i mennesker
- Pålidelig model
- Faciliterer studier der ikke kan udføres i mennesker – eller gnavere

Samarbejde

Thomas Emil Andersen
Lektor, Phd
Klinisk Mikrobiologisk afdeling
OUH



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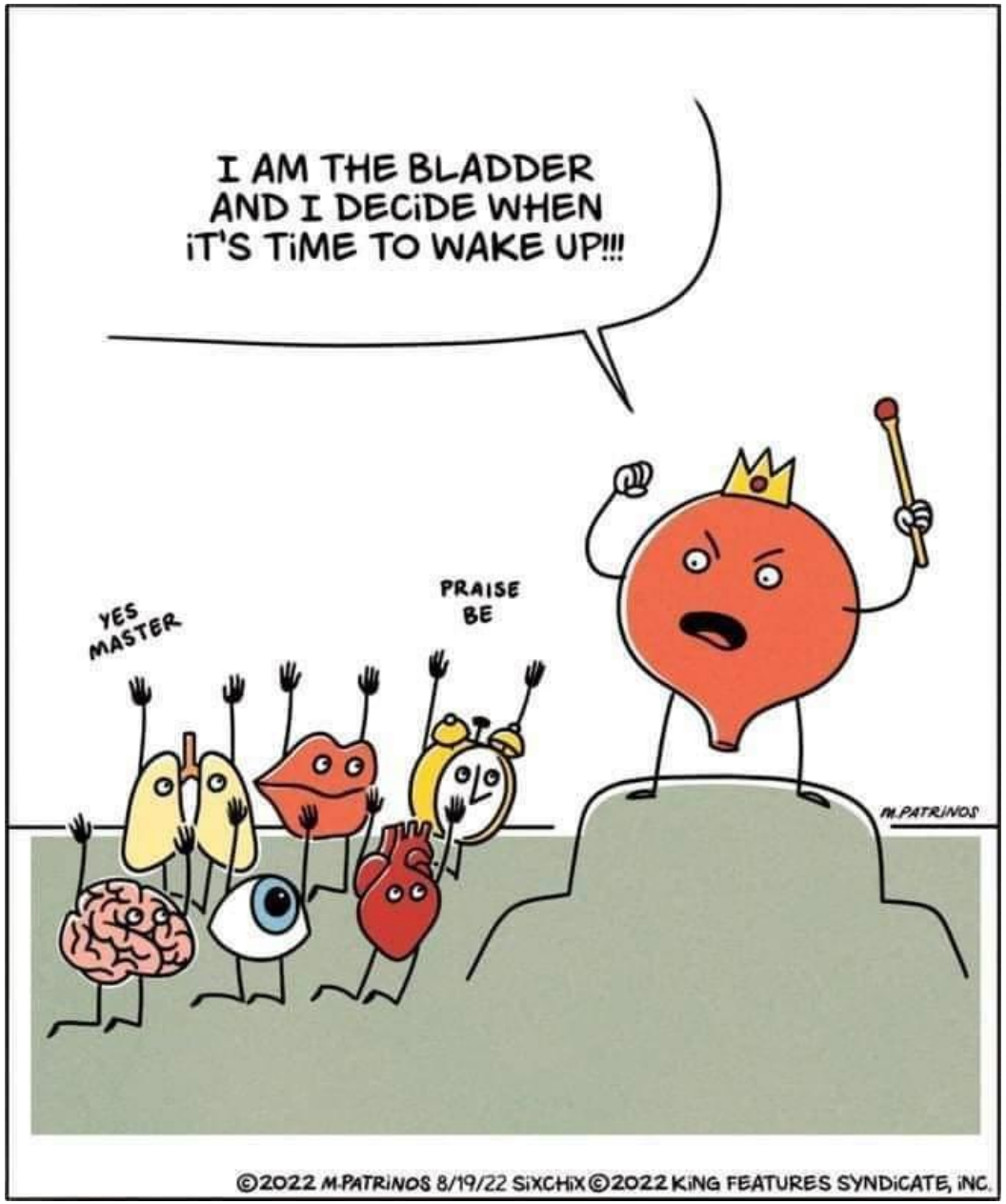
Syddansk Universitet

Yaseelan Palarasah
Lektor, Phd
Cancer og
Inflammationsforskning, SDU

Louise Kruse Jensen
Lektor, dr. med
Veterinærpatolog
Københavns Uni.

Spørgsmål?


I AM THE BLADDER AND I DECIDE WHEN IT'S TIME TO WAKE UP!!!
YES MASTER
PRAISE BE
M.PATRINOS
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