Synoptik-Fondens Pris

Fra Molekylær til Klinisk Oftalmologi
Fortid, Nutid og Fremtid

6. November 2022

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Øjenafdelingen
Aalborg Universitetshospital

Stor Tak til Synoptik-Fonden

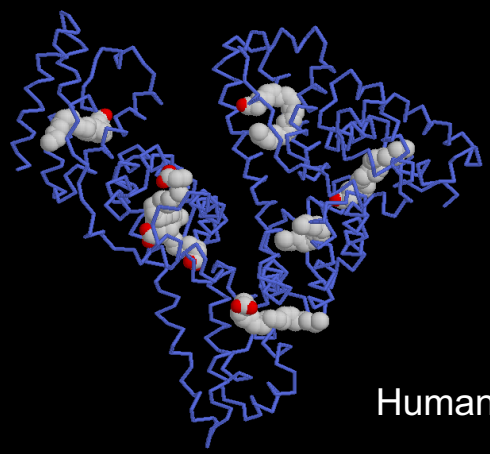
😀 😀 😀 😀

- MOLEKYLÆR OFTALMOLOGI
- TRANSLATIONEL OFTALMOLOGI
- KLINISK OFTALMOLOGI

MOLEKYLÆR OFTALMOLOGI

(Fortiden)

Engang proteiner altid proteiner !

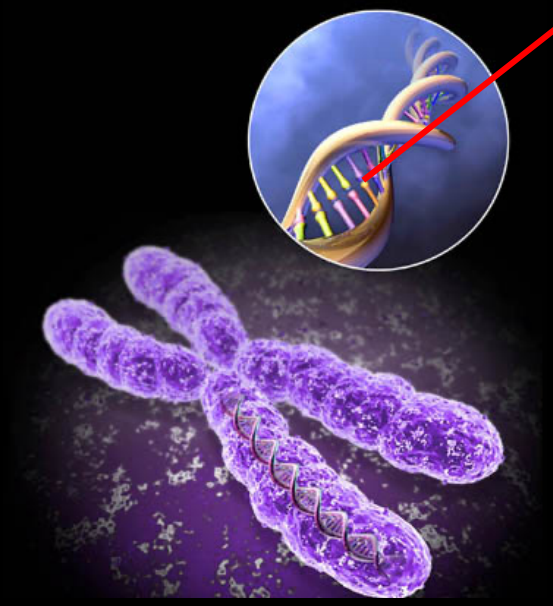


Human Serum Albumin

1994:
Ph.D. ”Fatty acid interaction with human serum albumin. Relation to diabetes, obesity, valproate-treatment, and anticoagulant therapy in surgery”.

1999:
Dr. med. ”Reversible ligand binding to human serum albumin - theoretical and clinical aspects".

De forskellige ”omer”



25.000 Genom

↓ Transkription

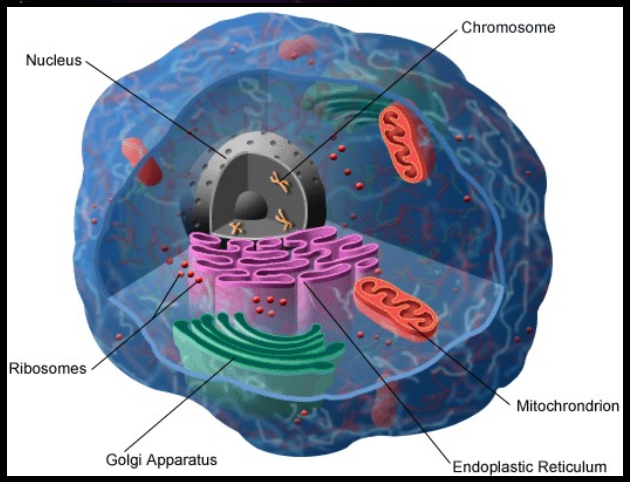
Transkriptom

↓ Translation

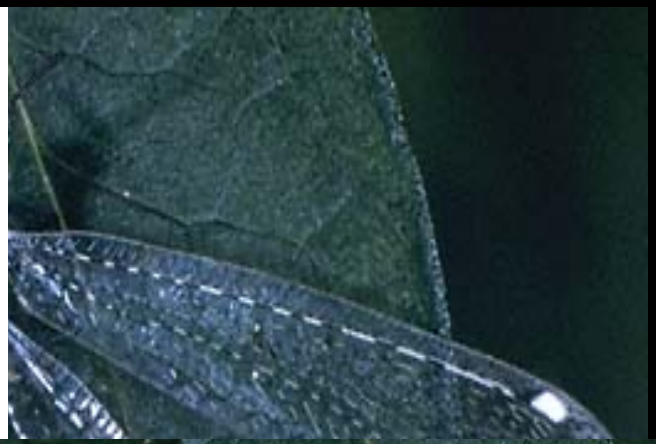
>1.000.000 Proteom

↓

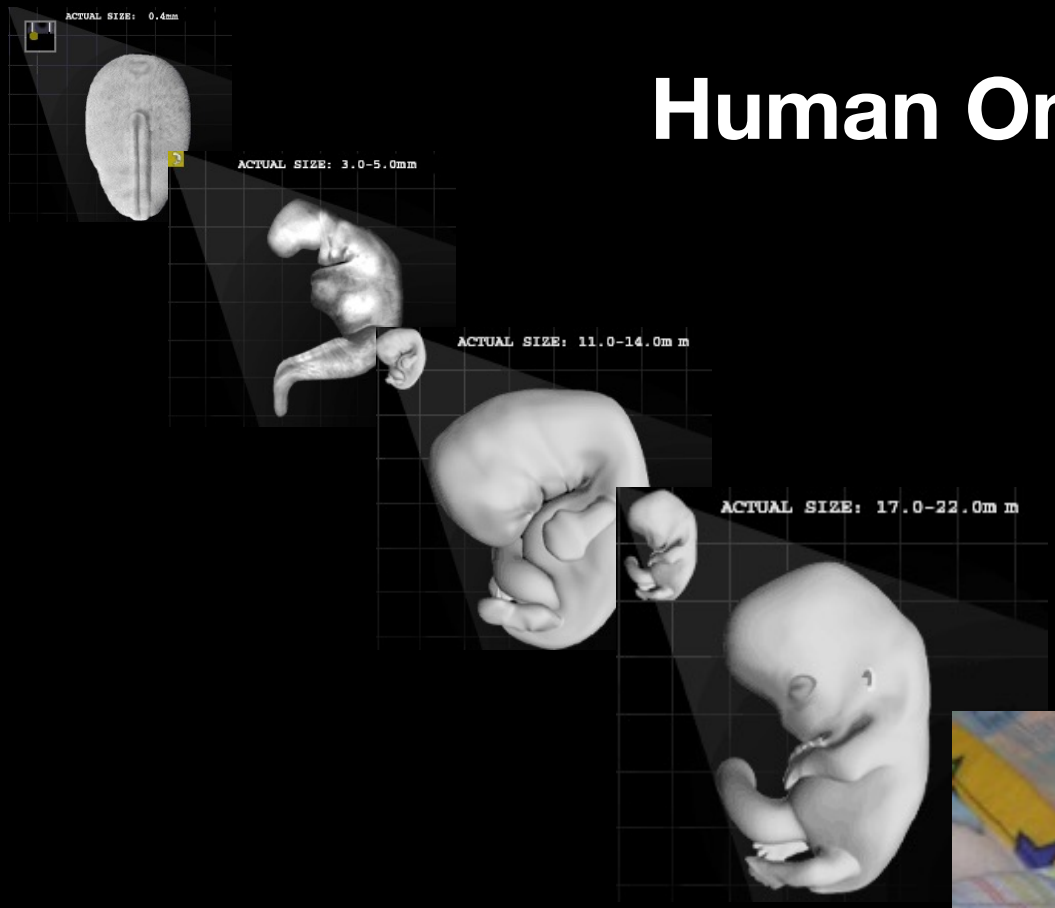
Omsætning af kulhydrat, fedt, protein, etc. **Metabolom**



Samme genom - forskelligt proteome



Human Ontogenese



Gel-baseret differentiel ekspressions proteomik

Sammenligning af en gruppe af celler/væv (Gruppe A)
med en anden gruppe af celler/væv (Gruppe B)

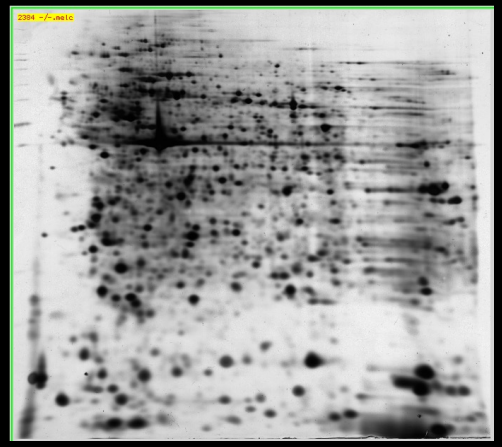
Gruppe A	*versus*	Gruppe B
Ubehandlede celler	*versus*	Behandlede celler
Udifferentierede celler	*versus*	Differentierede celler
Normale celler	*versus*	Transformerede celler

Gel-baseret differentiel ekspressions proteomik

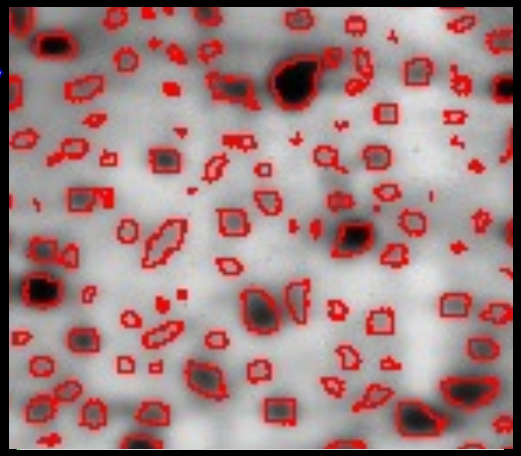
- Kørsel af et antal geler (4-6) af forskellige grupper (A, B, etc.)
- Gelerne sølvfarves og tørres
- Gelerne skannes på densitometer skanner (måler absorptionen i hver pixel)
- Hver gel analyseres af 2D software (fx Melanie eller PDQuest) til detektion og mængdebestemmelse af protein pletter

Sølvfarvet gel

Skannet gel

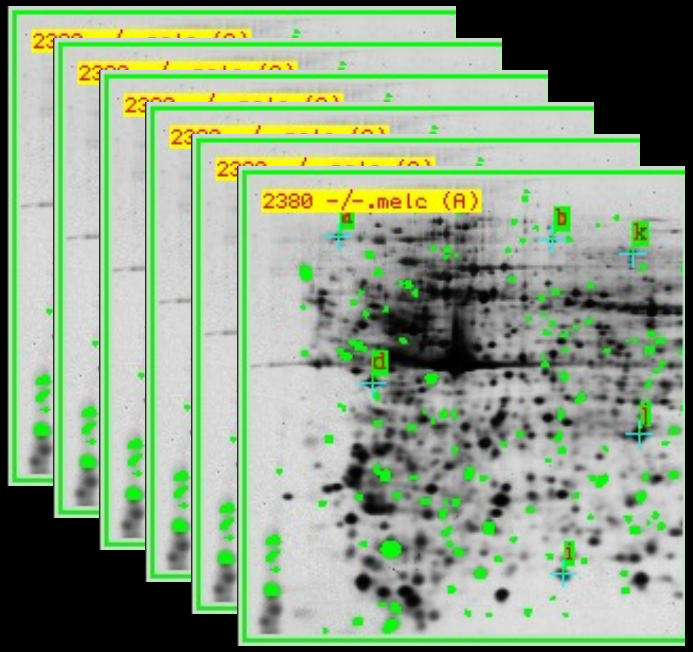


Kvantificerede spots

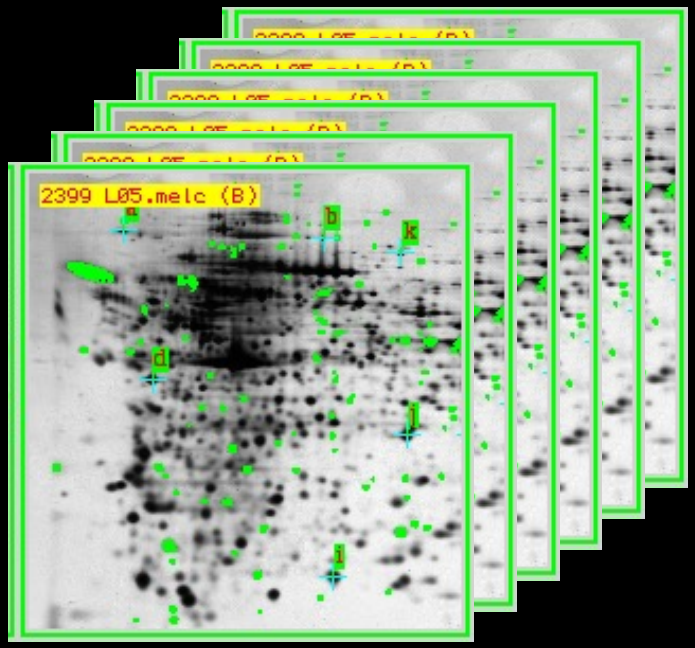


Computerassisteret sammenligning af de to grupper

Gruppe A

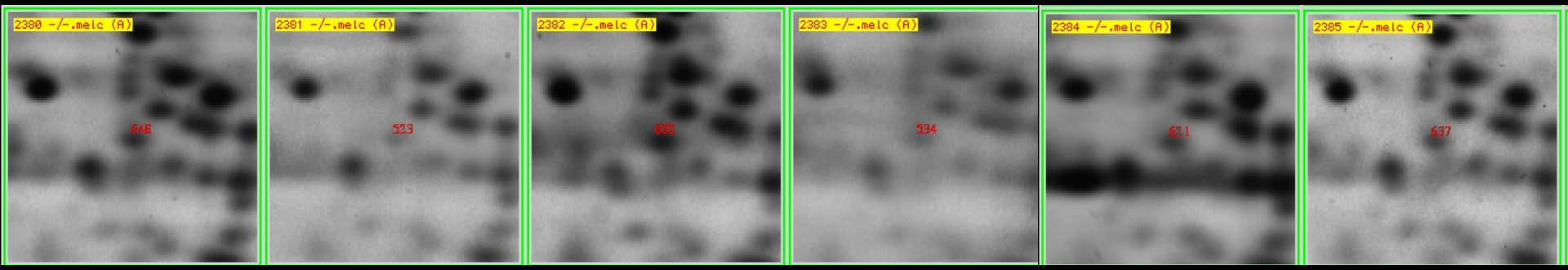


Gruppe B

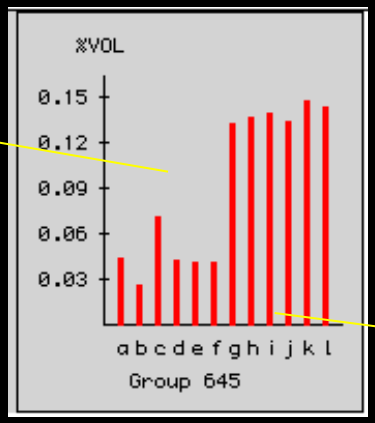


- Detektion af differentielt regulerede proteiner (signifikante)
- Selektion af signifikante proteiner med et vist ændringsniveau (fx >2 gange)

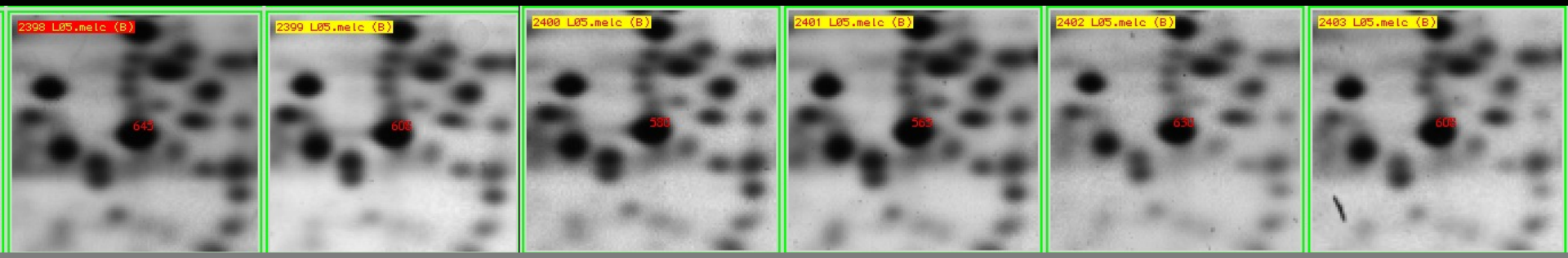
Opreguleret protein i gruppe B



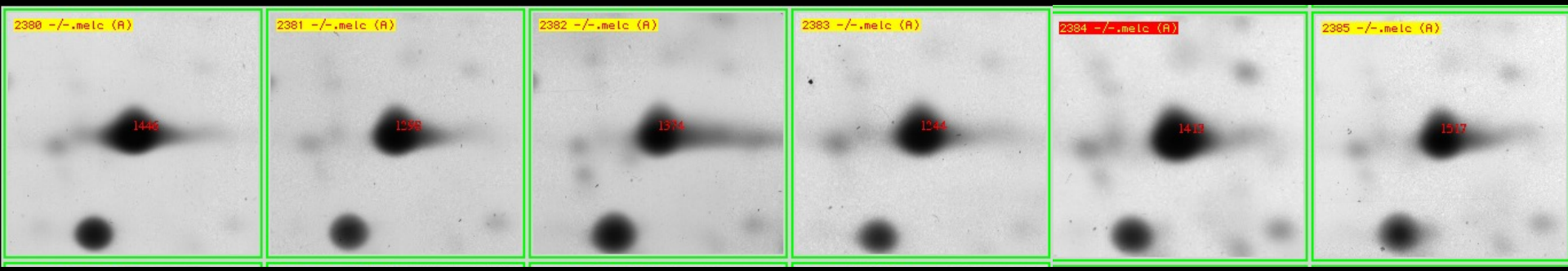
Gruppe A



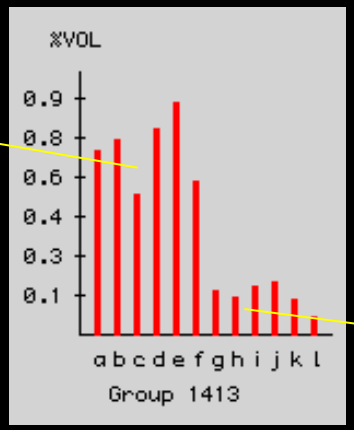
Gruppe B



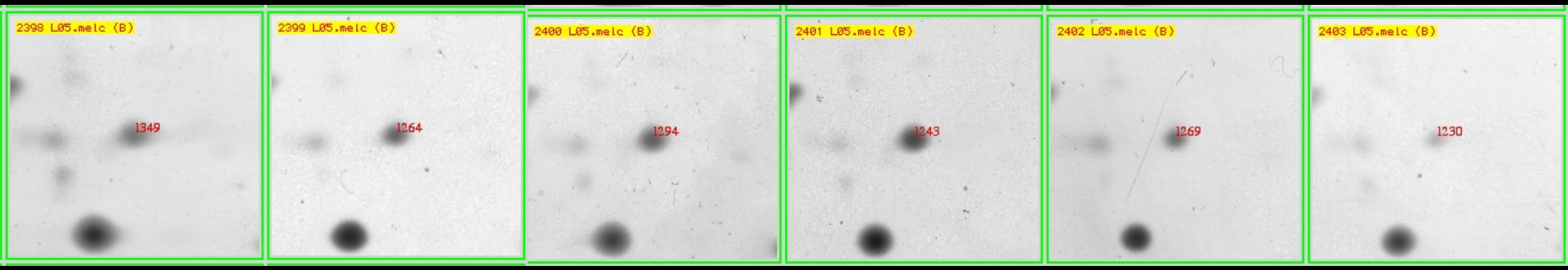
Nedreguleret protein i gruppe B



Gruppe A



Gruppe B



Massespektrometer

Okulære proteomstudier

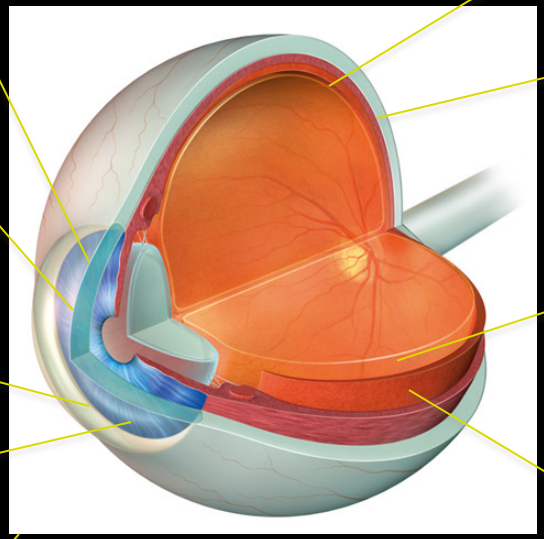
Acute corneal rejection
Funding *et al.*
Acta Ophthalmol. Scand. 83, 31-39, 2005

Marker proteins for keratoconus
Nielsen *et al.*
Exp. Eye Res. 82, 201-209, 2006

Stem cell markers
Lyngholm *et al.*
Exp. Eye Res. 87, 96-105, 2008

Cytokeratins
Lyngholm *et al.*
BMC Ophthalmol. 11, 3, 2011

Ocular proteomics in general.
Vorum et al. Biol Proced Online. 12: 56-88. (Review). 2009.

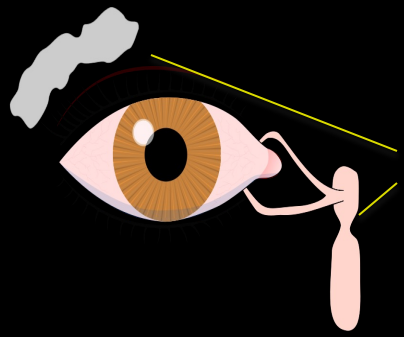


Lebers amaurosis
Vorum *et al.*
Proteome. Sci. 5, 5, 2007

Uveal melanomas
Coupland *et al.*
Invest. Ophthalmol. Vis. Sci. 51, 12-19, 2010

Retinal detachment in rabbits
Mandal *et al.*
Mol. Vis. 17, 2634-2648 2011
(PhD-project finalized 2011)

Hyperclycemia
Mandal *et al.*
(in preparation) 2012



Lacrimal gland and eyelid
Vorum et al.
Ann. Anat. 193, 469-478, 2011

Okulære proteomstudier

Corneal rejection

Funding *et al.*
Acta Ophthalmol. Scand. 83, 234-239, 2005

Funding *et al.*
Acta Ophthalmol. Scand. 83, 234-239, 2005

Keratoconus

Nielsen *et al.*
Corne. 24, 661-668, 2005

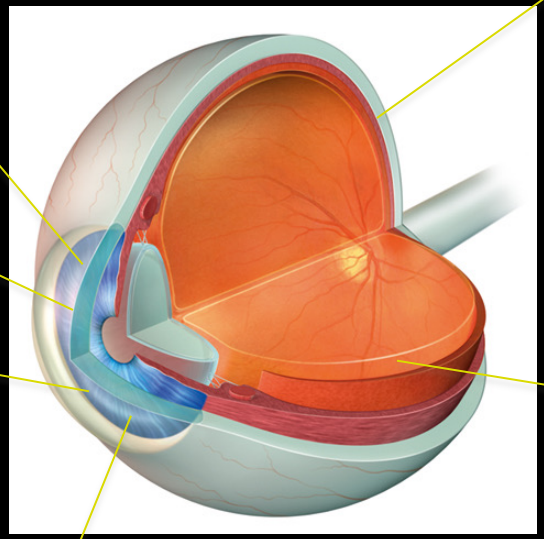
Stem cell markers

Lyngholm *et al.*
Exp. Eye Res. 87, 115-121, 2008

Bath *et al.*
Stem Cell Res. 10, 349-360, 2013

Bath *et al.*
Plos One. 8, 64244, 2013

Bath *et al.*
Mol. Vis 12, 797-803 2014



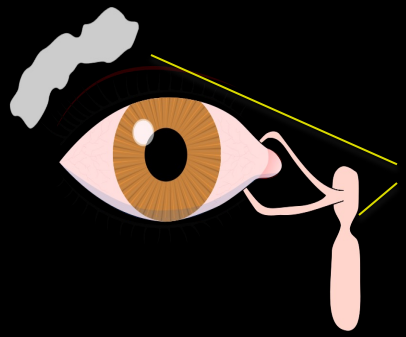
AMD

Ilginis et Vorum
Acta Ophthalmol. 90, 487-488, 2012

Retinal detachment in rabbits

Mandal *et al.*
Acta Ophthalmol. 91, 333-334 2013

Mandal et al.
J. Ophthalmol. 15, 58304, 2015



Lacrimal gland tear film

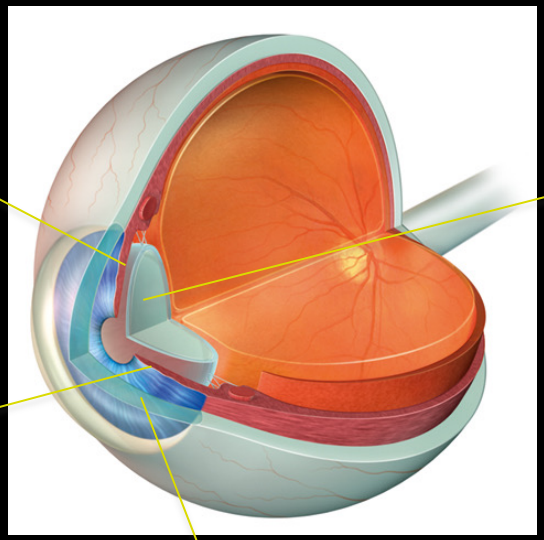
Nielsen et Vorum
Ancta Ophyhalmol. 93, 658-662, 2015

Okulære proteomstudier

Fuchs Endothel dystrophy

Poulsen *et al.*
J. Proteom Res. 13, 4659-4667, 2014

Poulsen *et al.*
Proteomics Clin. Appl . 8, 168-177, 2014



Cataract

Clemmensen *et al.*
Graefes Arch. Clin. Exp. Ophthalmol.
225, 119-125, 2017

Cornea dystrophies

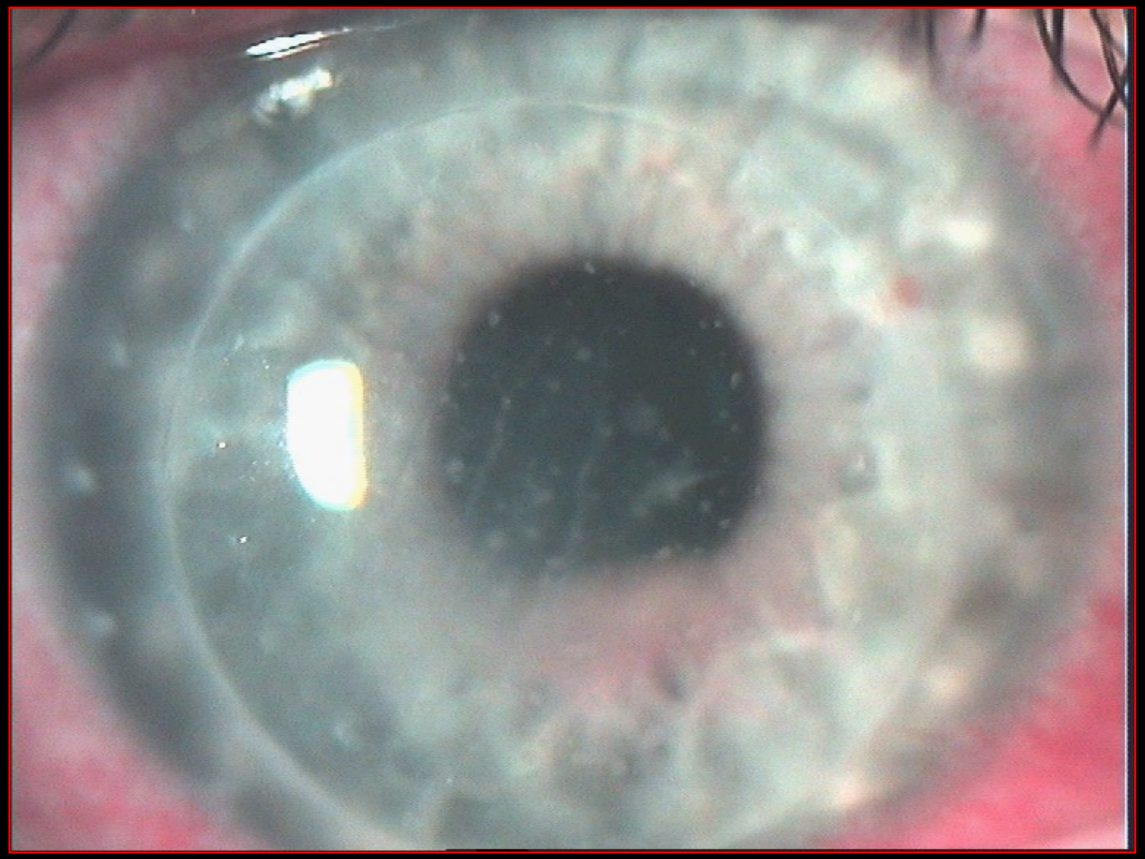
Poulsen *et al.*
FEBS. J. 285, 101-114, 2018

Poulsen *et al.*
j. Biol, Chem. 2, 11817-11828, 2019

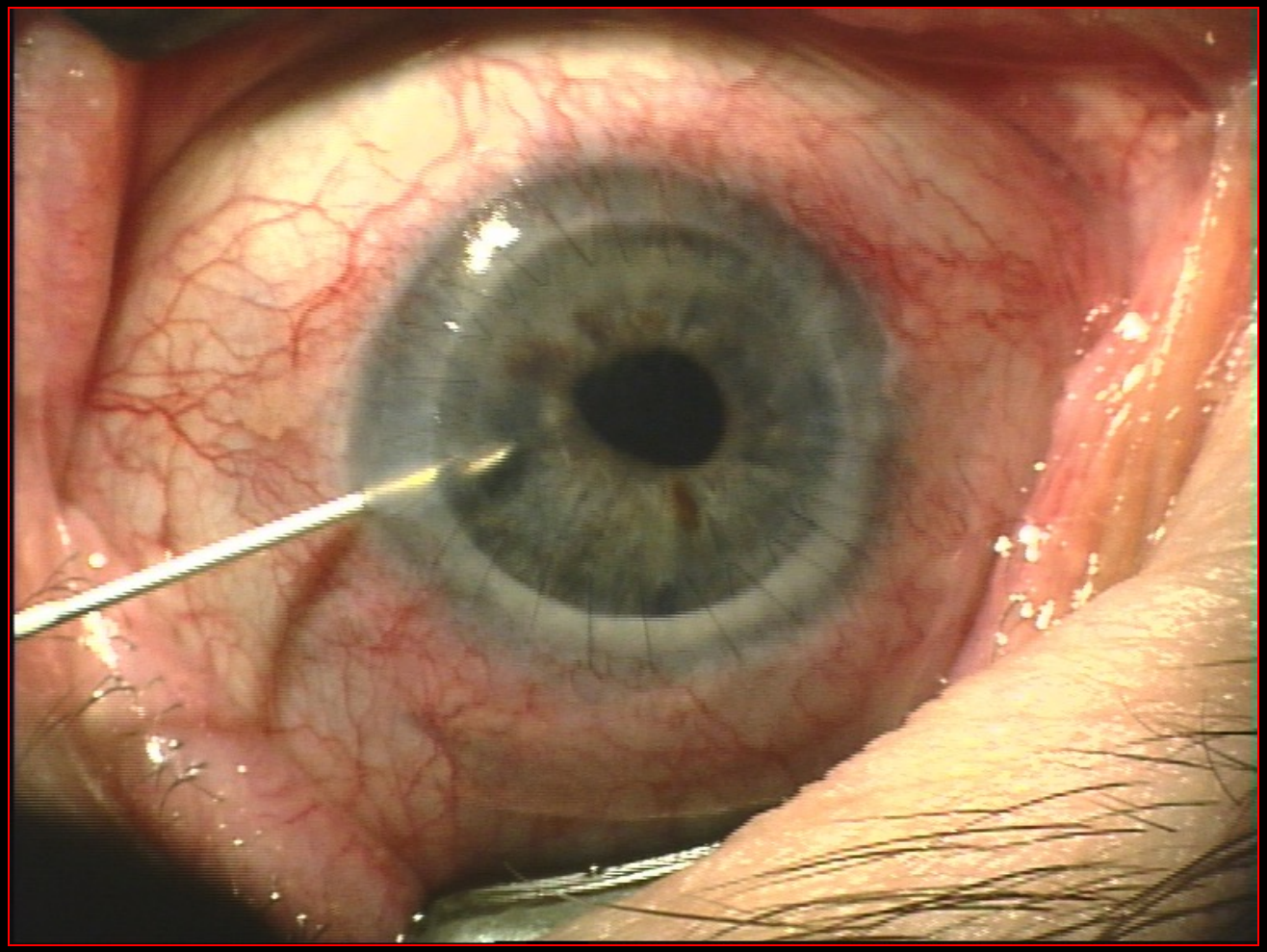
Human cornea proteom

Dyrlund, Vorum, Enghild. J. Proteom Res..
11: 4231-4239, 2012.

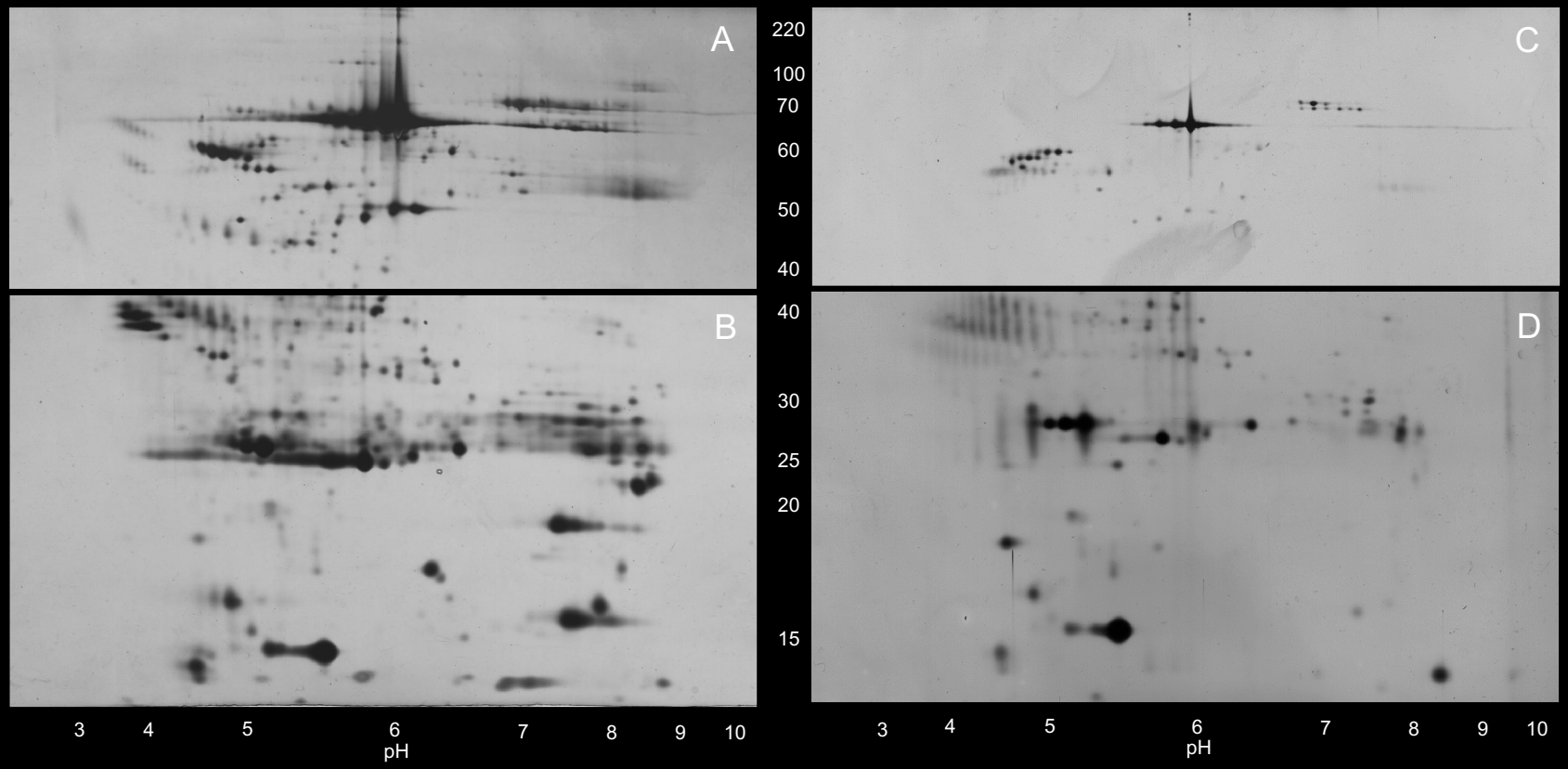
Proteomanalyse af kammervæske ved cornea-transplantat afstødning



Paracentese



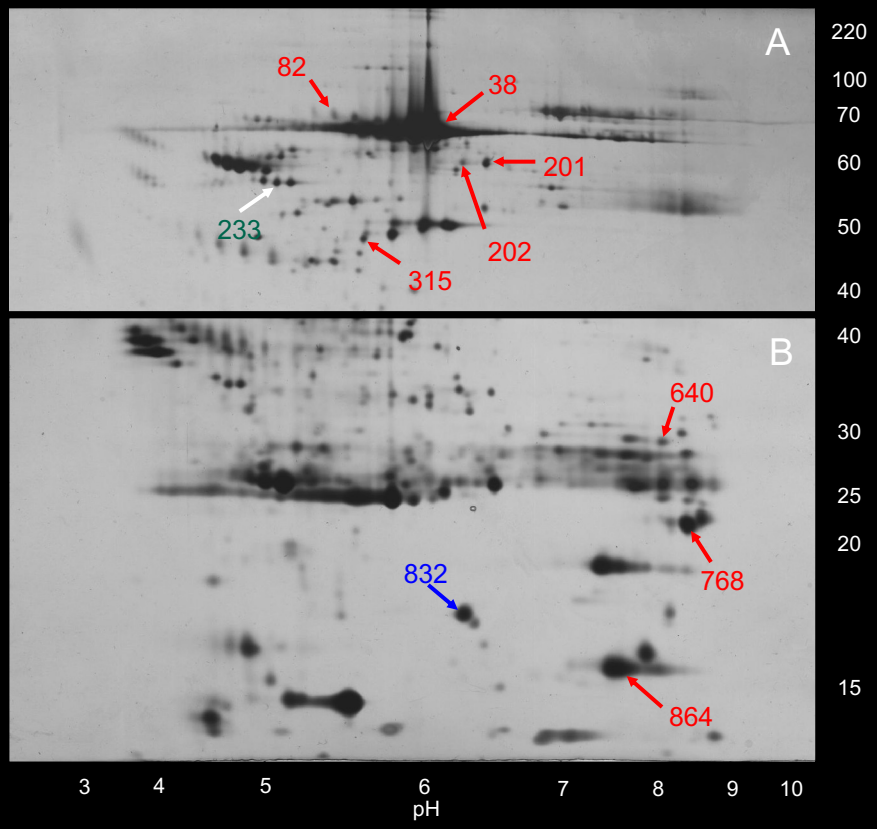
Forskellig proteinprofil



Rejection

Cataract

Korrigerede spot volumes



- 10 spots var signifikant forhøjet:

  8 fragmenter af albumin

  Cytokeratin type II

  Alfa-1-antitrypsin

Funding et al. Acta Ophtalmol Scand, 83: 31-39, 2005

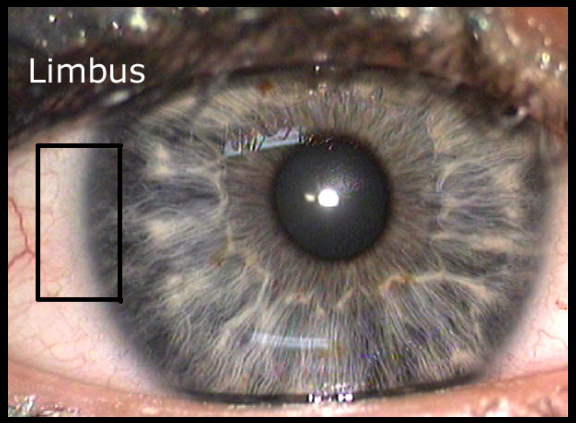
Funding et al. Acta Ophtalmol Scand, 83: 234-239, 2005

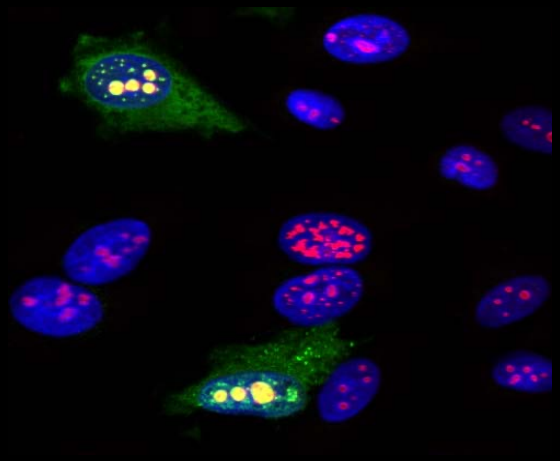
Funding et al. Acta Ophtalmol Scand, 83: 379-384, 2005

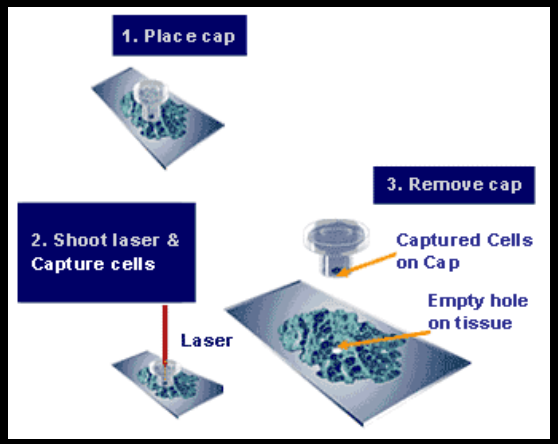
Konklusion

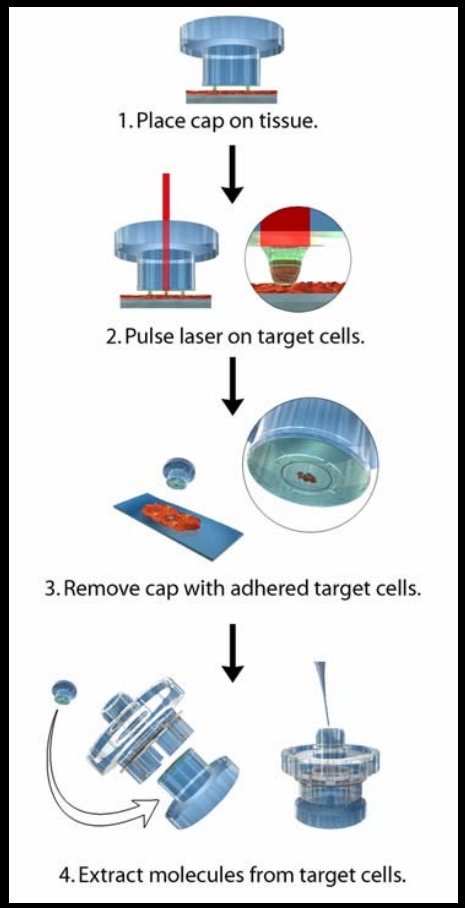
- Kammervæskens proteinsammensætning ændres under corneal afstødning.
- Der ses en intraokulær produktion af alfa-1-antitrypsin, som har en mulig gavnene effekt på den corneale rejektion.

Corneale limbale stamceller:









Dyrlund, Vorum *et* Enghild. *J Proteome Res.* 11: 4231-4239. 2012.

TRANSLATIONEL OFTALMOLOGI

(Nutid)

Retinal veneokklusion

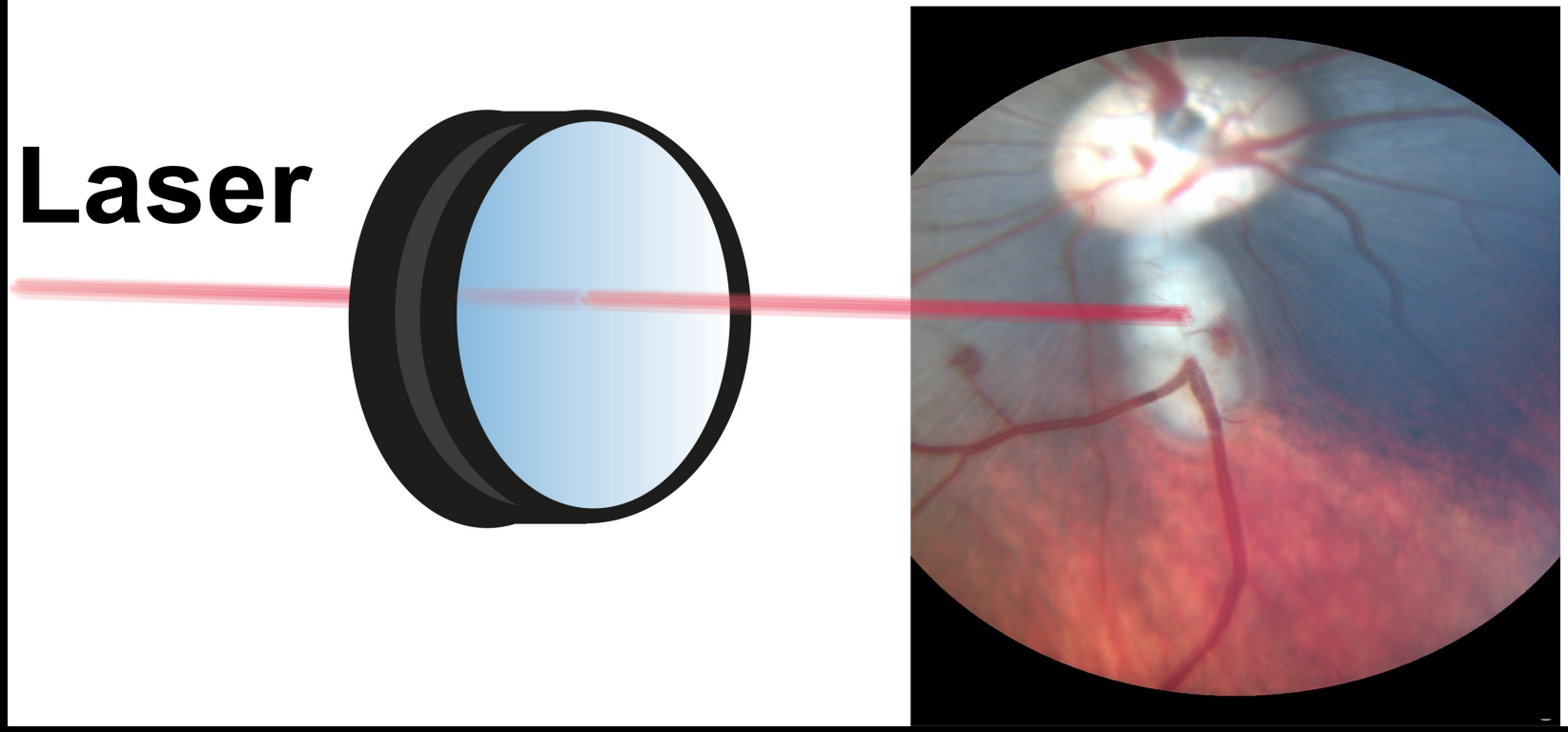
Formål

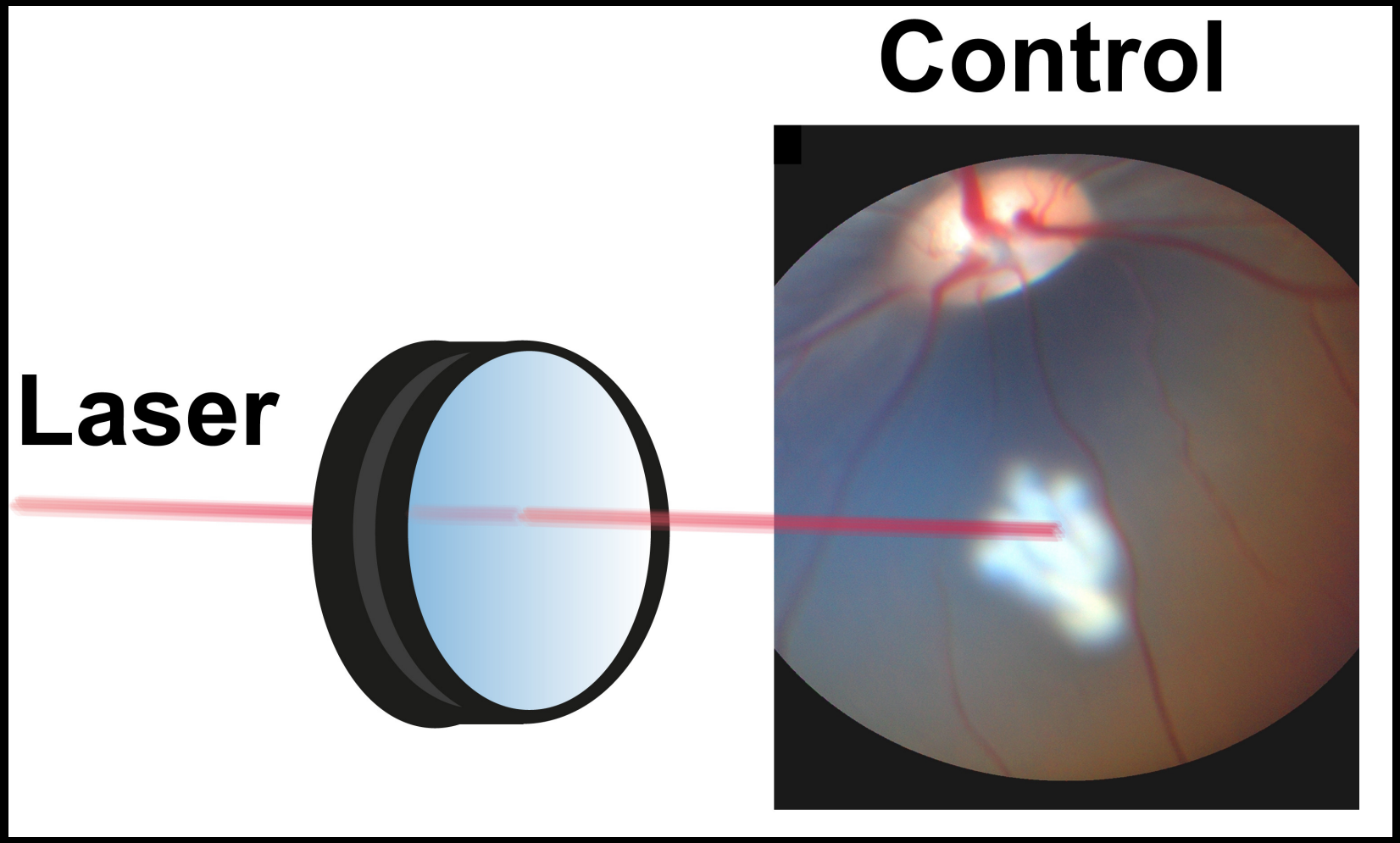
Identifikation af nye angrebspunkter

for behandling

Experimental retinal vein occlusion

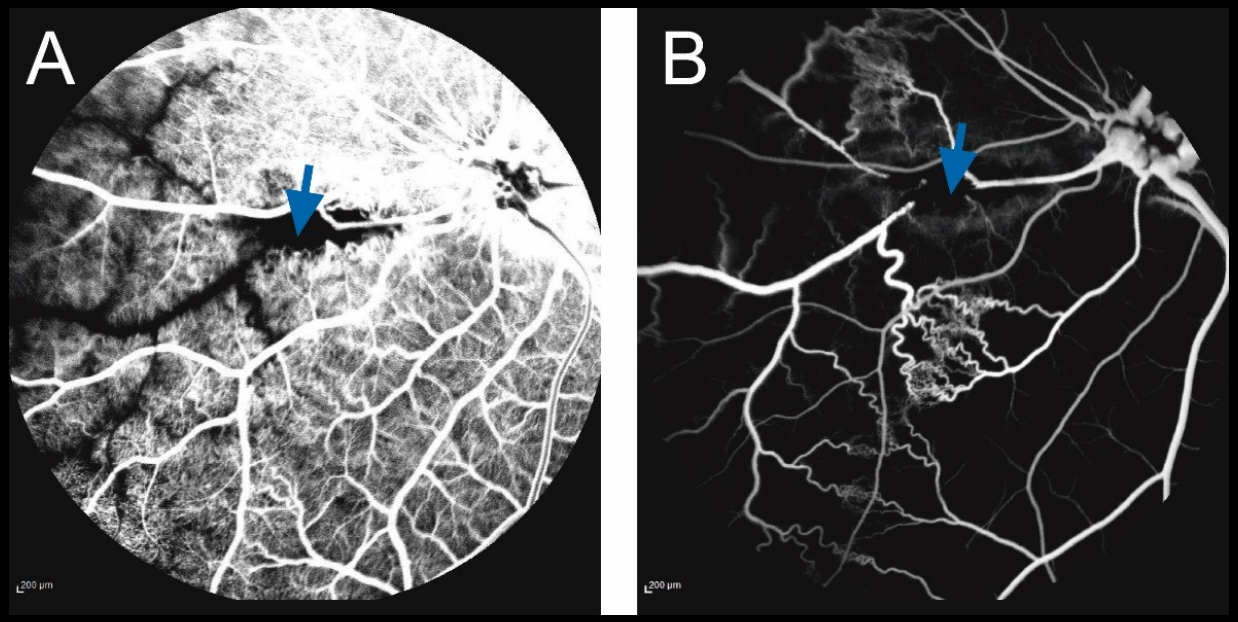
Experimental vein occlusion



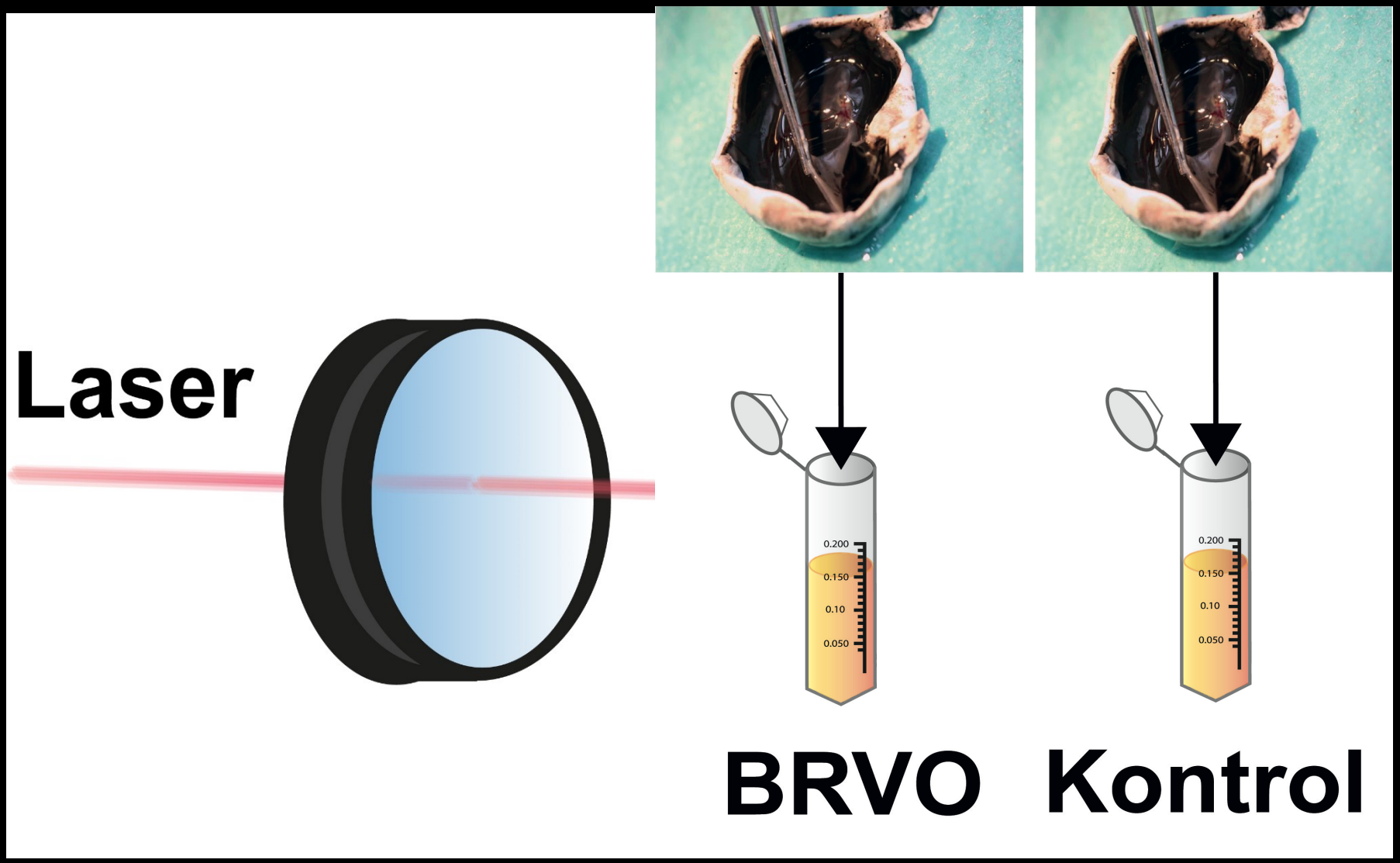

Control
Laser

Experimental vein occlusion

Cehofski LJ, Vorum H et al. Exp. Eye Res., 2018
Cehofski LJ, Vorum H et al., Exp. Eye Res., 2015

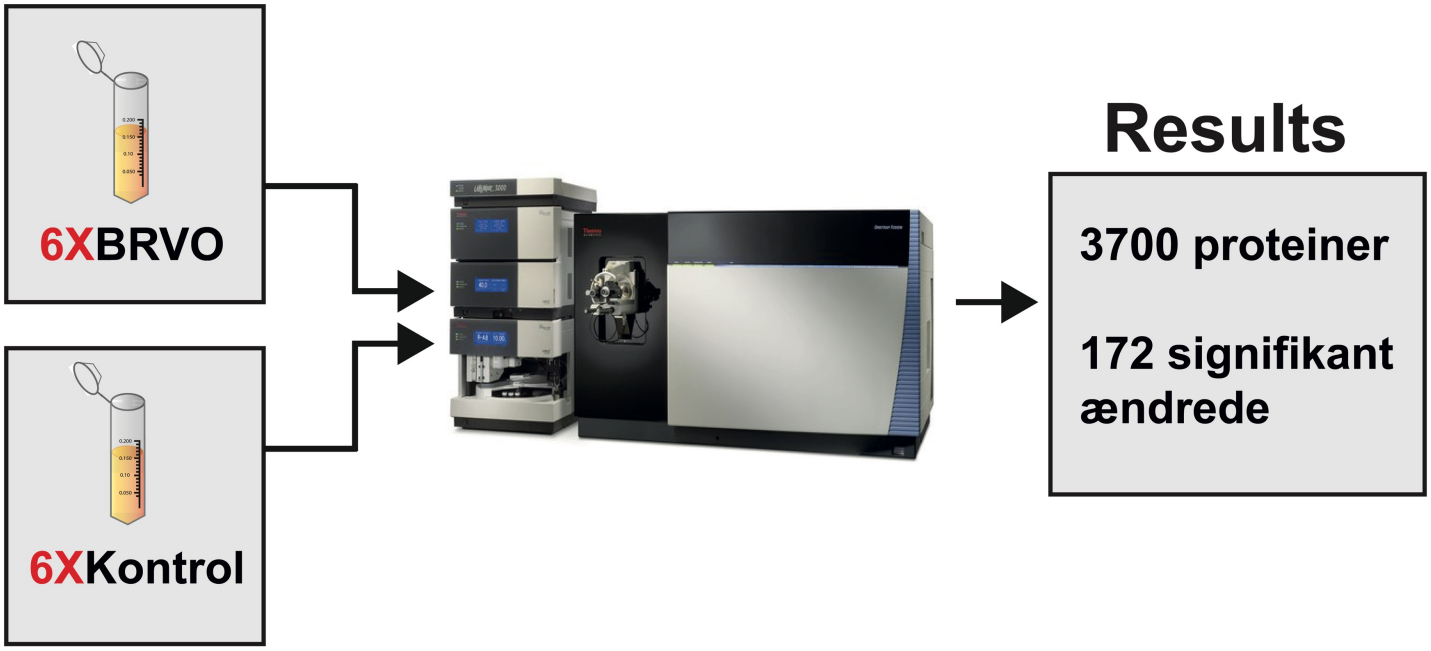


Cehofski LJ, Vorum et al., J Ophthalmol, 2015
Cehofski LJ, Vorum et al., Exp Eye Res, 2015



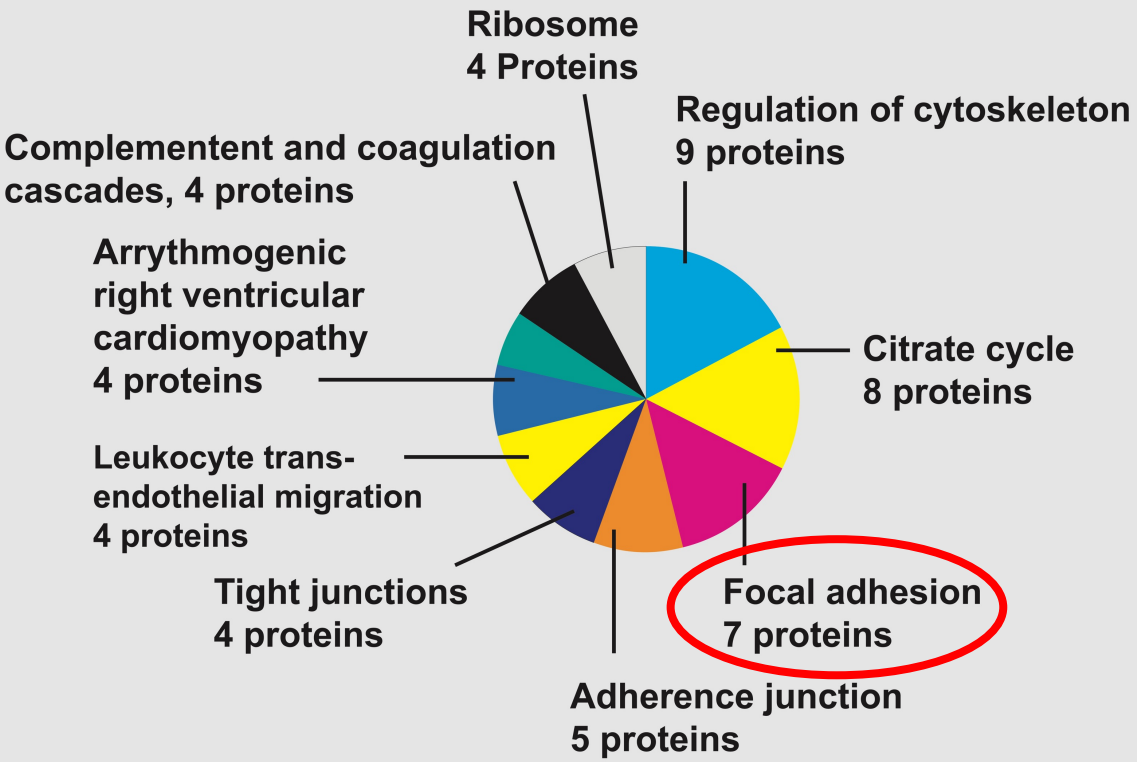
Cehofski LJ, Honoré B, Vorum H et al., Experimental Eye Research, 2016

BRVO vs. kontrol

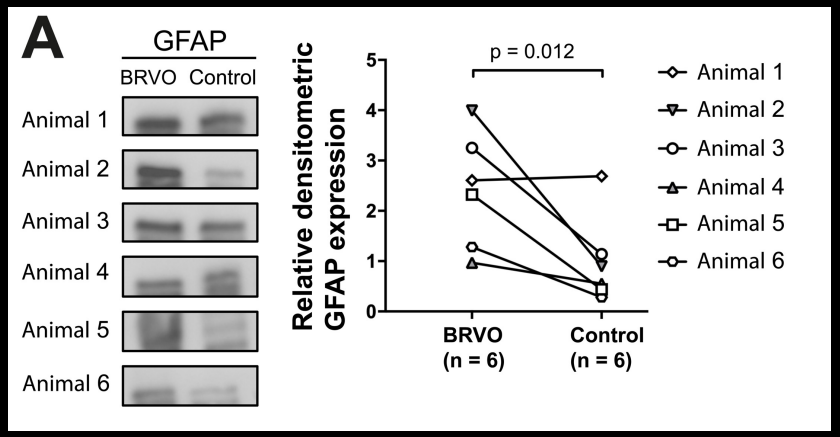


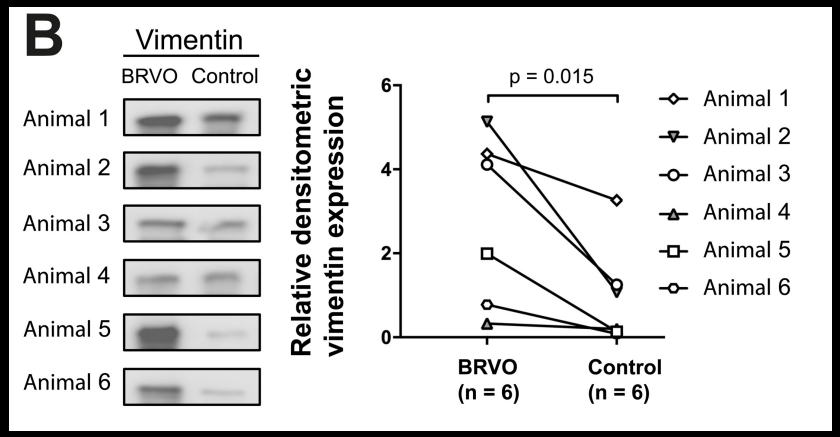
Cehofski LJ, Honoré B, Vorum H et al., Experimental Eye Research, 2015
Cehofski LJ, Honoré B, Vorum H et al., Experimental Eye Research, 2020

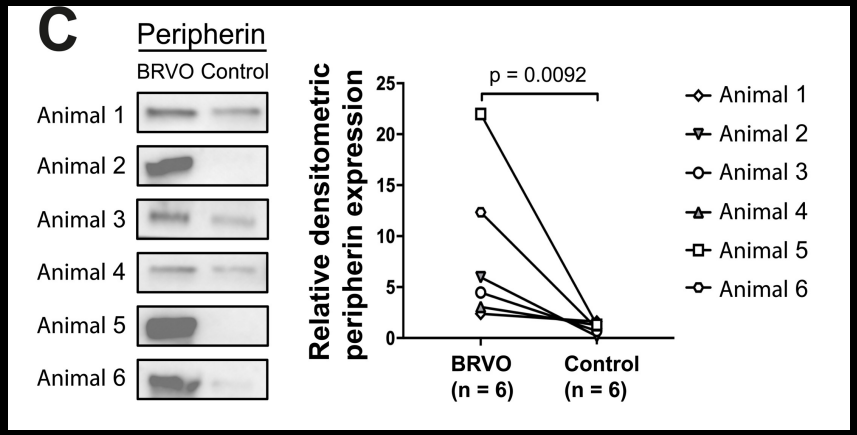
Aktiverede signalveje - BRVO



Cehofski LJ, Honoré B, Vorum H et al., Experimental Eye Research, 2015
Cehofski LJ, Honoré B, Vorum H et al., Experimental Eye Research, 2019

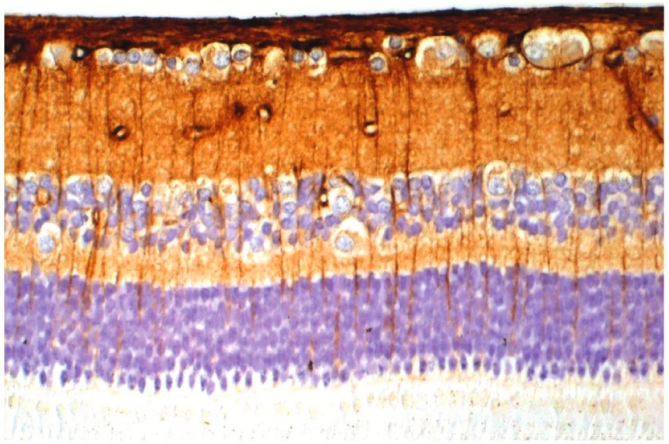

A
GFAP
BRVO Control
Animal 1
Animal 2
Animal 3
Animal 4
Animal 5
Animal 6
Relative densitometric GFAP expression
p = 0.012
0
1
2
3
4
5
BRVO (n = 6)
Control (n = 6)
Animal 1
Animal 2
Animal 3
Animal 4
Animal 5
Animal 6


B
Vimentin
BRVO Control
Animal 1
Animal 2
Animal 3
Animal 4
Animal 5
Animal 6
Relative densitometric vimentin expression
p = 0.015
0
2
4
6
BRVO (n = 6)
Control (n = 6)
Animal 1
Animal 2
Animal 3
Animal 4
Animal 5
Animal 6

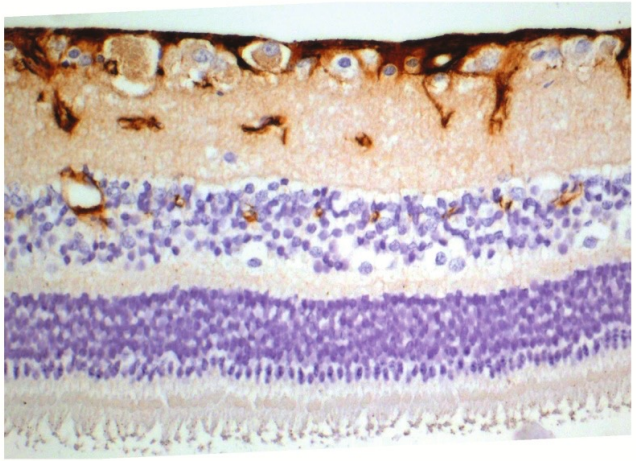

C
Peripherin
BRVO Control
Animal 1
Animal 2
Animal 3
Animal 4
Animal 5
Animal 6
Relative densitometric peripherin expression
p = 0.0092
0
5
10
15
20
25
BRVO (n = 6)
Control (n = 6)
Animal 1
Animal 2
Animal 3
Animal 4
Animal 5
Animal 6

Müller cell stress

RVO
GFAP



Control
GFAP



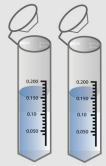
KYOTO PREFECTURAL UNIVERSITY OF MEDICINE
京都府立医科大学
Department of Ophthalmology／眼科

Kammervandsprøver

BRVO prøver (n = 23)

Inklusion:
BRVO
Makulært ødem
Ingen behandling
Ødem < 3 mdr.

Eksklusion
Neovaskulært glaukom
Diabetes
Irisrubeosis
Brug af øjendråber

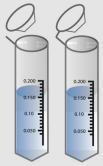


vs.

Kontrolprøver (n = 17)

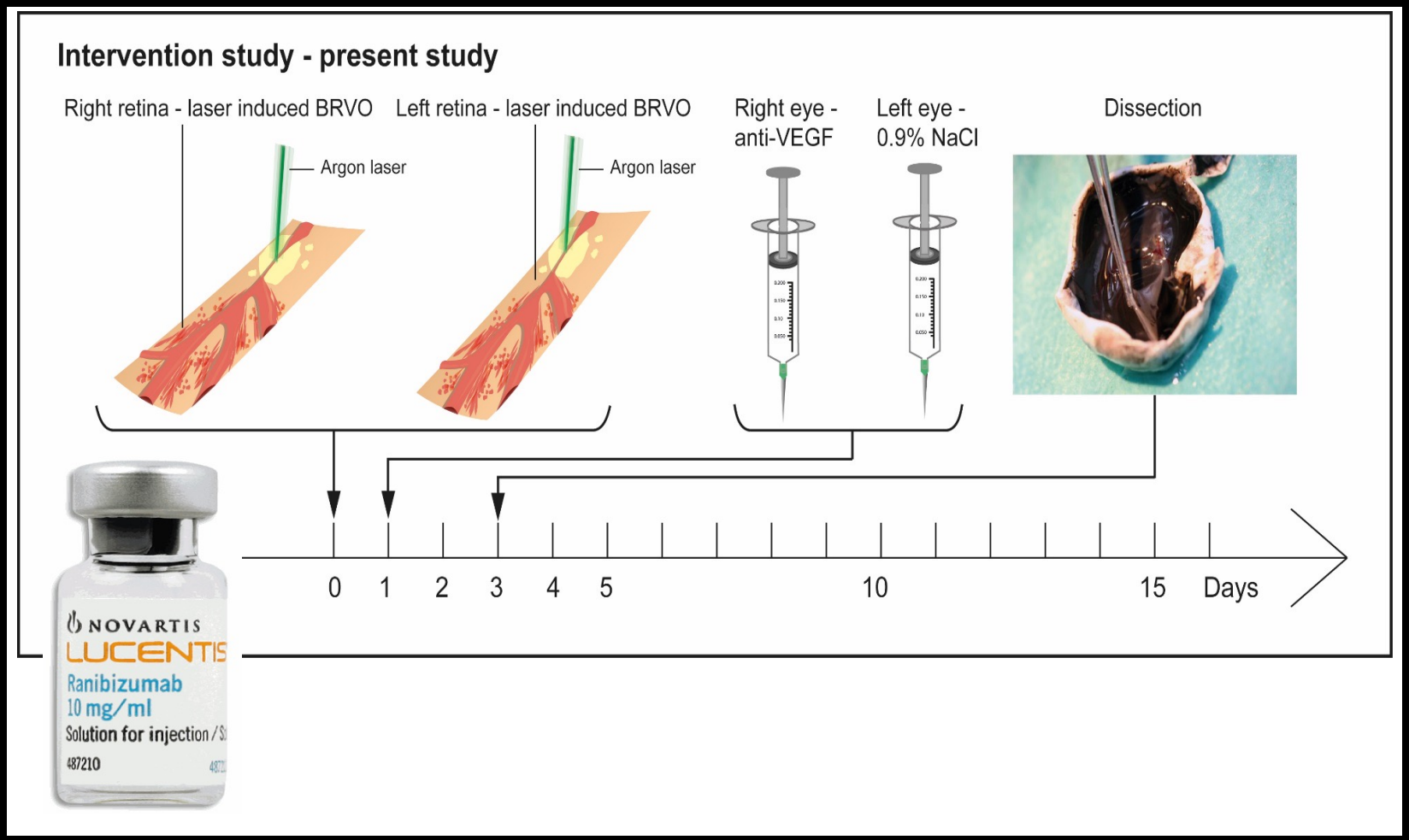
Inklusion:
Aldersmatchede
Før kataraktkirurgi

Eksklusion
Anden okulær sygdom end katarakt



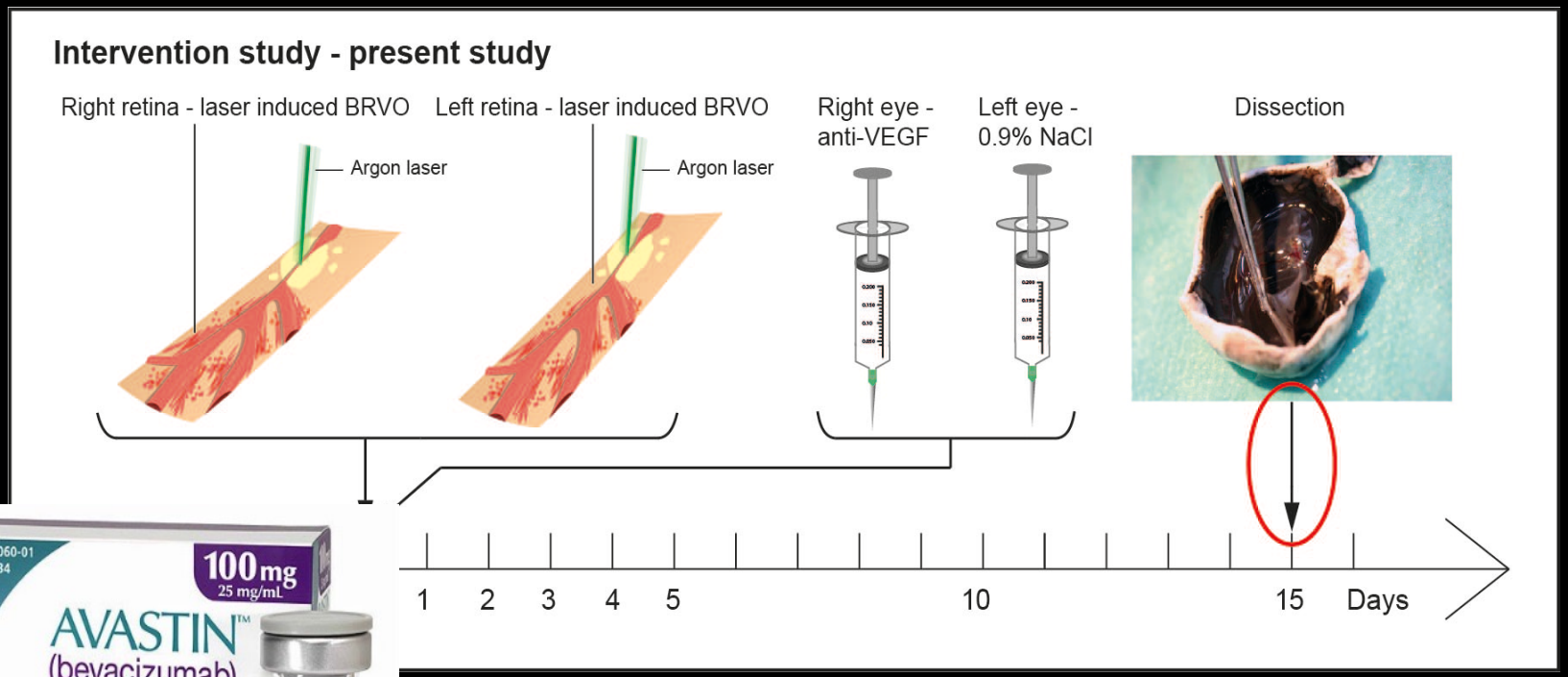
Proteomics

Anti-VEGF interventions



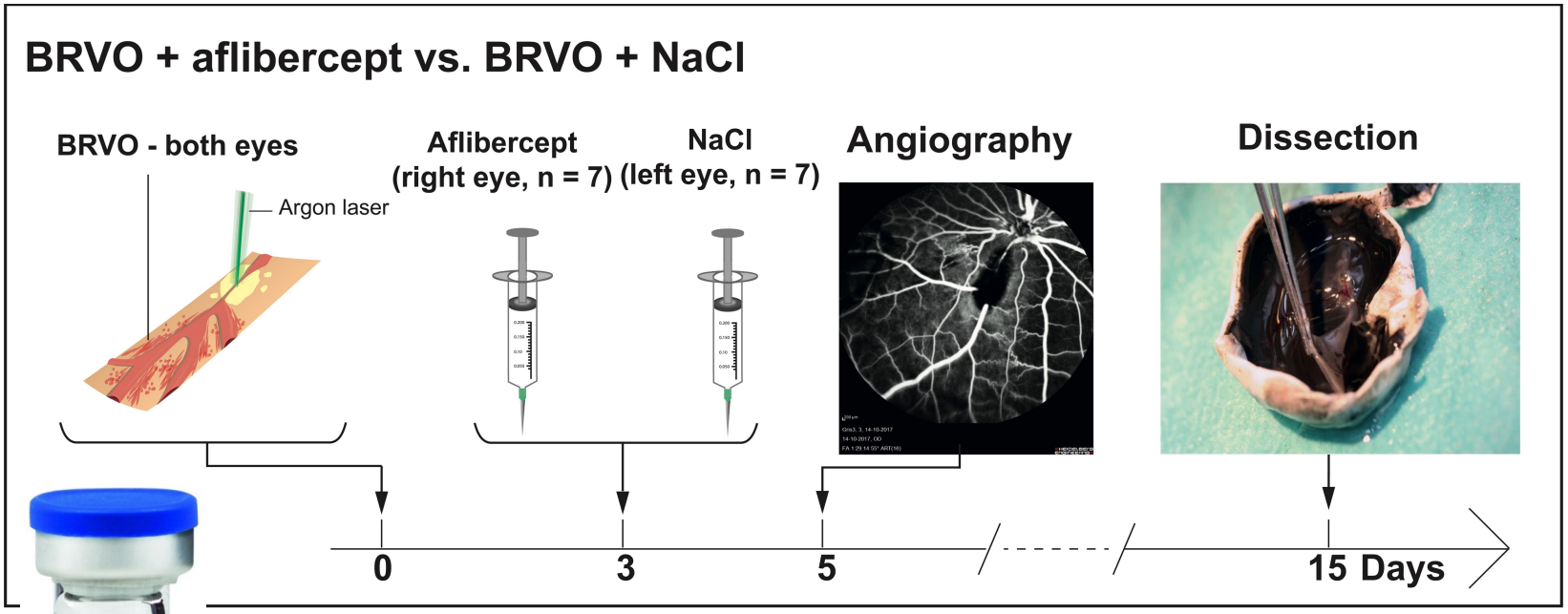
Cehofski LJ, Vorum H et al., Exp. Eye Res., 2016

Anti-VEGF behandling



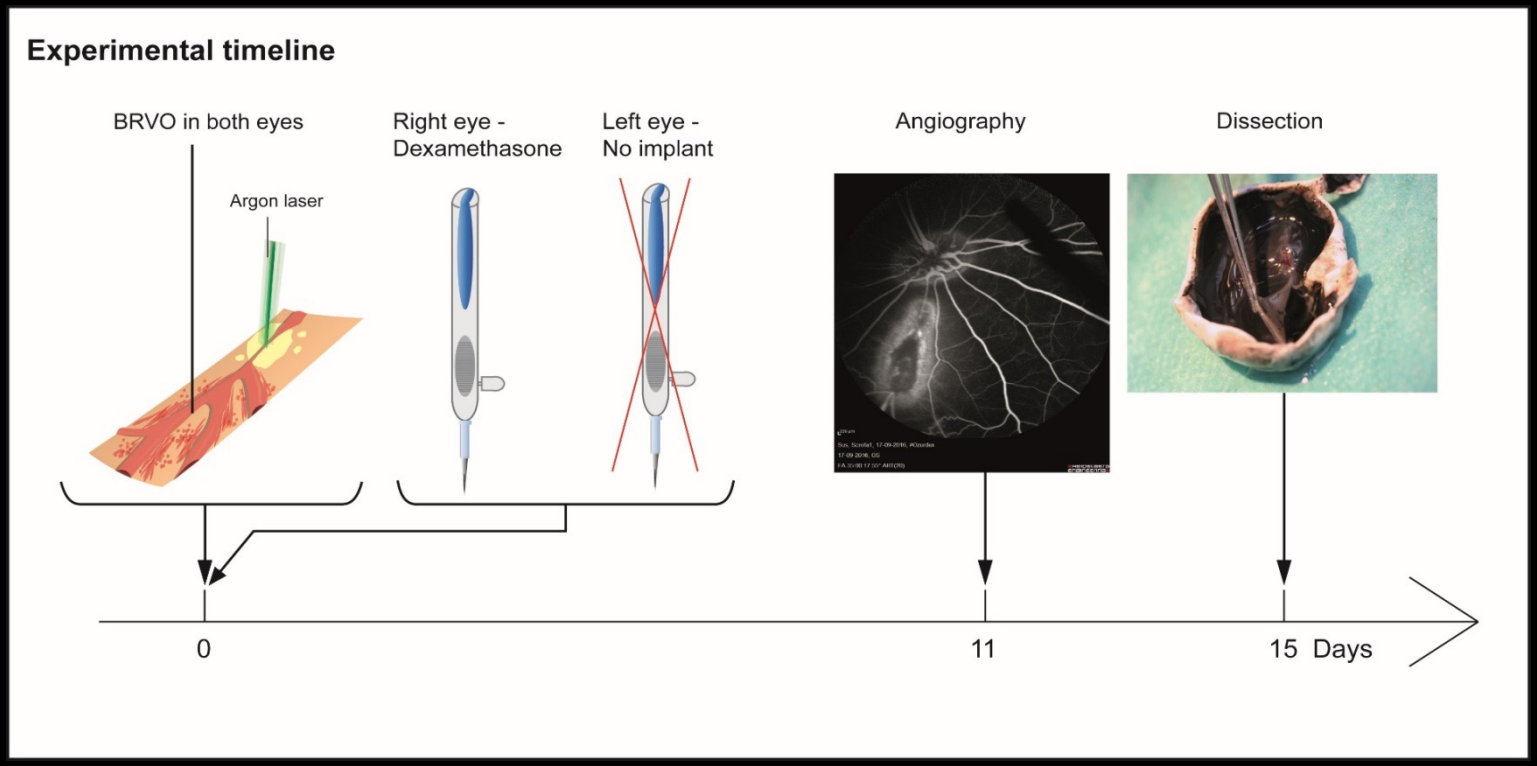
Cehofski LJ, Vorum et al., Mol. Vis., 2018

Anti-VEGF behandling



Cehofski LJ, Vorum H et al., submitted, 2019

Ozurdex behandling



Cehofski LJ, Vorum H et al., Exp. Eye Res., 2018

BRVO + intervention

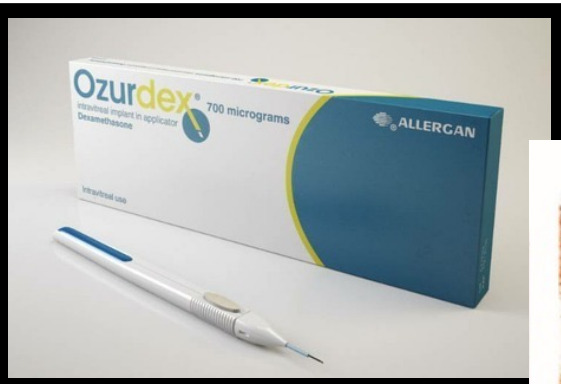
Når retina på 2 dage

Transthyretin stiger

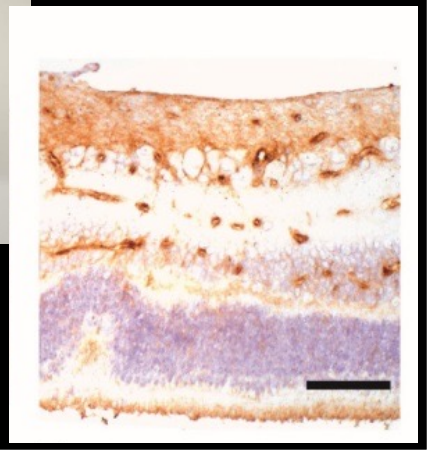
Regulering af

andre signalveje

begrænset



Caveolin-1



KLINISK OFTALMOLOGI

(Fremtid)

Retinale Vaskulære Okklusioner

Forekomst og dødelighed

RAO

Incidens (CRAO)
1.8 per 100.000 PY[1]

Øget stroke-relateret dødelighed[3]

RVO

Incidens
15 per 100.000 PY[2]

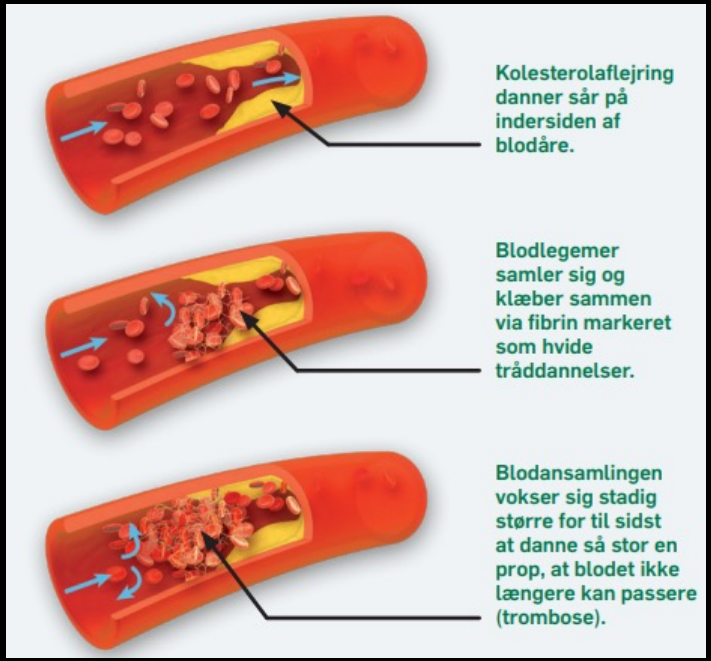
Øget dødelighed3

1 Park SJ, Choi N-K, Seo KH, Park KH, Woo SJ. Nationwide incidence of clinically diagnosed central retinal artery occlusion in Korea, 2008 to 2011. Ophthalmology. 2014 Oct;121(10):1933–8.

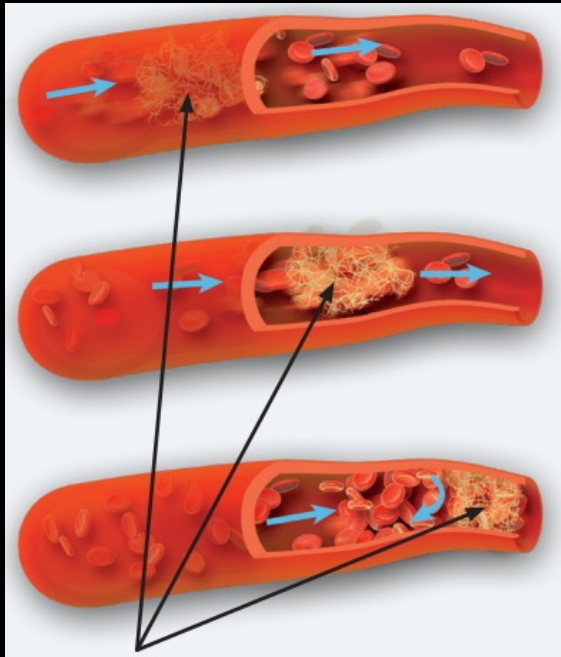
2 Toft-Petersen AP, Muttuvelu D V, Heegaard S, *et al.* Correlation between retinal vein occlusion and cancer - a nationwide Danish cohort study. *Acta Ophthalmol* 2018;96:800–3. doi:10.1111/aos.13860.

3 Bertelsen M, Linneberg A, Christoffersen N, *et al.* Mortality in patients with central retinal vein occlusion. *Ophthalmology* 2014;121:637–42. doi:10.1016/j.ophtha.2013.07.025

TROMBOSE - BLODPROP

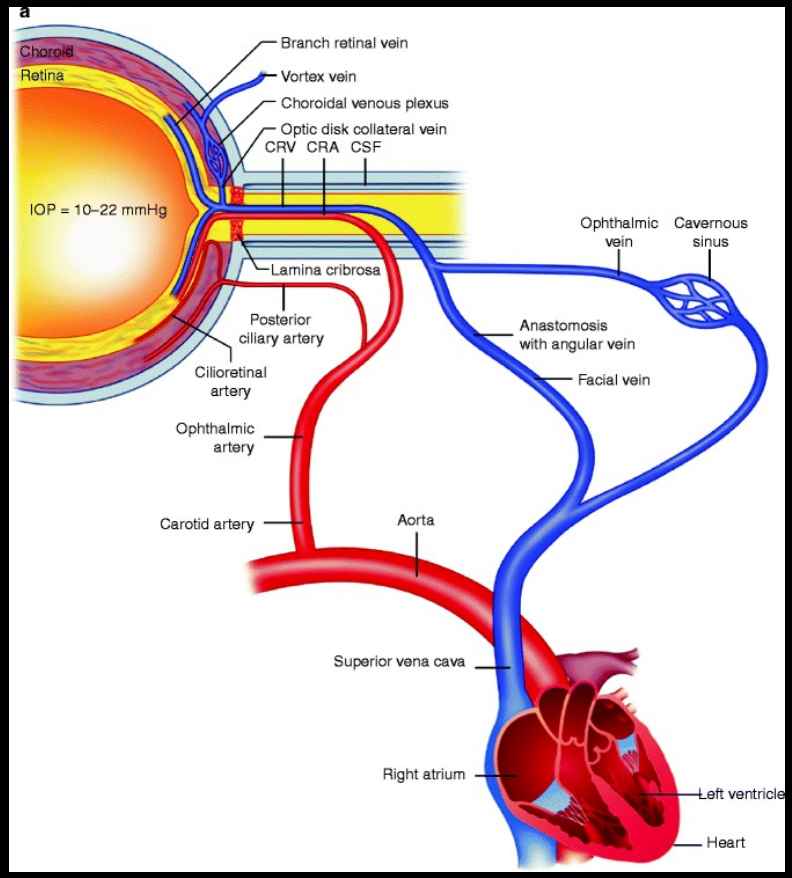


EMBOLI - BLODPROP



En løsrevet trombosesektion fra den del af blodåren, som er relativt bred i diameter, føres videre gennem blodåren, der gradvist snævrer ind. Når blodåren bliver tilpas snæver, kiler sektionen sig fast, så blodgennemstrømningen stoppes. Denne form for blodprop kaldes en emboli.

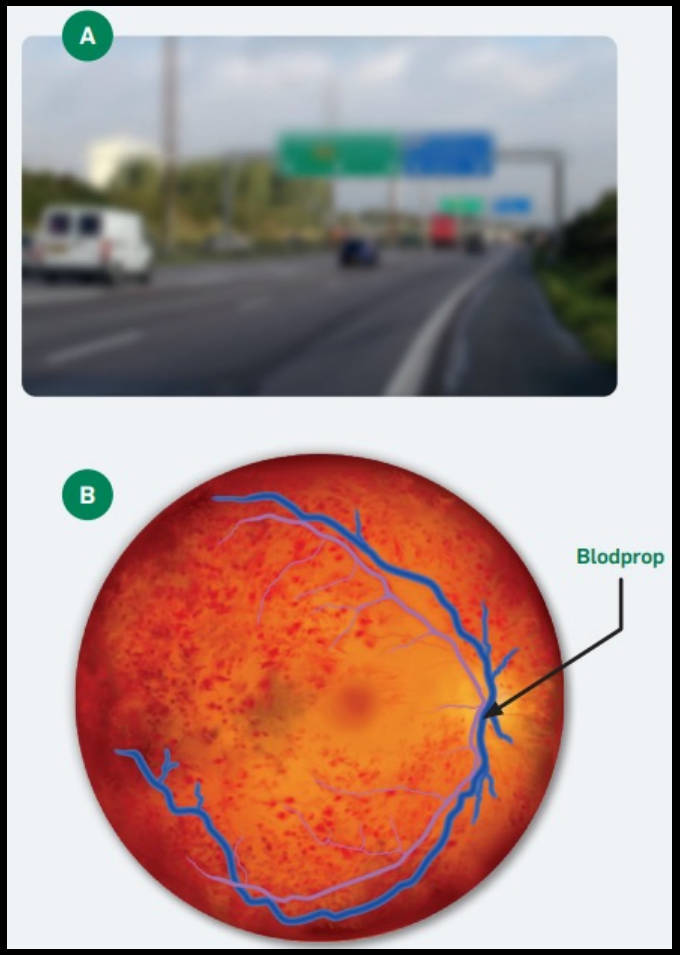
”EYE and HEART”



Venøs blodprop i nethinden

Ca. 19.000 danskere rammes hvert år af en veneblodprop i øjet

Påvirkning af hele synsfeltet tyder på blodprop i den centrale vene
Påvirkning af en del af synsfeltet tyder på blodprop i en grenvene i nethinden



Arteriel blodprop i nethinden

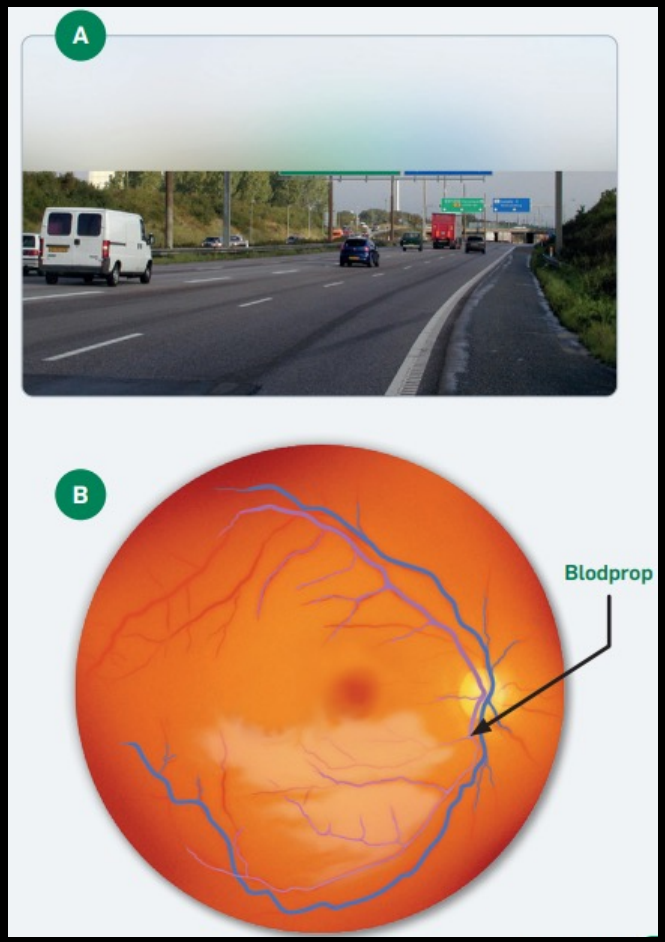
Ca. 400 danskere rammes hvert år af en arteriel blodprop i øjet

Mister synet på del af synsfeltet

Iskæmi der svarer til det afficerede område

Permanent synstab

Ingen behandling



Papers

Ørskov M, Vorum H, Larsen TB, Lip GYH, Bek T, Skjøth F. (2022) Clinical risk factors for retinal artery occlusions: a nationwide case-control study. *International Ophthalmology*.

Ørskov M, Vorum H, Larsen TB, Lip GYH, Bek T, Skjøth F. (2022) Evaluation of risk scores as predictive tools for stroke in patients with retinal artery occlusion: A Danish nationwide cohort study. *TH Open. (In press)*

Ørskov M, Vorum H, Larsen TB, Lip GYH, Bek T, Skjøth F. (2022) Retinal artery occlusion as an early indicator of macrovascular complications in diabetes. *American Journal of Medicine*.

Papers

Ørskov M, Vorum H, Bjerregaard Larsen T, Vestergaard N, Lip GYH, Bek T, Skjøth F. (2022). A review of risk factors for retinal vein occlusions. *Expert Rev Cardiovasc Ther*.

Ørskov M, Vorum H, Larsen TB, Lip GYH, Bek T, Skjøth F. (2022) Similarities and Differences in Systemic Risk Factors for Retinal Artery Occlusion and Stroke: A Nationwide Case-Control Study. *J stroke Cerebrovasc Dis*.

Ørskov M, Vorum H, Larsen TB, Lip GYH, Bek T, Skjøth F. (2022) Similarities and differences in systemic risk factors for retinal artery occlusion and retinal vein occlusion: A nationwide case-control study. *Int Ophthalmol*.

Ørskov M, Nissen TPH, Vorum H, Larsen TB, Skjøth F. (2022) Positive prediction value of retinal artery occlusion diagnoses in the Danish National Patient Registry: a validation study *(submitted).*

De nationale sundhedsregistre

Lang tradition for registre

Store mængder data

CPR-nummer

Fuld dækning - fra vugge til grav

	Danish Registries
1870	Danish Twin Registry
1925	Danish Registry of Cerebral Paresis
1937	Registry of Tuberculosis
1943	Danish Cancer Registry; Registry of Causes of Death
1949	Danish Multiple Sclerosis Registry; Military Conscription Registry
1968	Danish Civil Registration System; Cytogenic Register
1969	Central Psychiatric Registry
1970	Income Statistics Register; Suicide registry
1973	Medical Birth Registry; Register of Legally Induced Abortions
1974	Student Register
1976	Danish Breast Cancer Cooperative Group Database; Employment Classification Module
1977	Danish National Patient Registry
1979	Central Register of Labour Market Statistics; Aarhus Sarcoma Registry
1980	Intregated Database for Labour Market Research; Fertility Database
1981	Population's Education Register; Building and Housing Register
1982	Danish Pacemaker and ICD Registry
1983	Danish Register of Congenital Malformations
1985	Danish Registry of Childhood Cancer; Melanoma Database
1989	Regional Prescription Databases; Register for Suicide Attempts; National Vascular Registry
1990	Nephrology Registry; National Health Service Register; Laboratory Database
1994	Danish Colorectal Cancer Database; In Vitro Fertilisation Register
1995	Danish National Prescription Database; Hip Athroplasty Registry
1996	Danish Multiple Sclerosis Treatment Registry
1997	Danish Transfusion Database; Pathology Database; Knee Arthroplasty Registry
1999	Western Denmark Heart Registry
2000	Danish Heart Registry; Acute Leukemia Registry; Rheumatology Database; Lung Cancer Database; Bladder Cancer Database
2002	Danish Database for Hepatitis B and C
2003	Danish Stroke Registry; Heart Failure Registry; Schizophrenia Database; Lymphoma Database
2004	Danish Database of Reimbursed Prescriptions; Hysterectomy Database; Anesthesia Database; Geriatry Database
2005	Danish Cruciate Ligament Registry; Gynecological Cancer Database; Myelomatosis Database
2006	Danish National Diabetes Registry; Shoulder Alloplasty Registry; Pancreatic Cancer Database
2007	Danish Intensive Care Database; GP Database; Non-Melanoma Skin Cancer Database; COPD Database
2008	Danish Cervical Cancer and Mammography Screening Databases; Fetal Medical Database
2009	Danish Sarcoma Database; Children's Cancer Database; Neuro-Oncology Database
2010	Danish Prostate Cancer Database; Renal Cancer Database; Sleep Apnea Database; Organ Donation Database
2011	Danish Penile Cancer Database; Depression Database; ADHD Database; Ocular Oncology Database
2013	Danish Testicular Cancer Database; Heart Rehabilitation Database; Liver and Bile Cancer Duct Cancer Database
2014	Danish Colorectal Cancer Screening Database

Registre brugt i dette projekt

CPR-registeret

Landspatientregisteret

Lægemiddelstatistikregisteret

Danish Registries	
1870	Danish Twin Registry
1925	Danish Registry of Cerebral Paresis
1937	Registry of Tuberculosis
1943	Danish Cancer Registry; Registry of Causes of Death
1949	Danish Multiple Sclerosis Registry; Military Conscription Registry
1968	**Danish Civil Registration System**
1969	Central Psychiatric Registry
1970	Income Statistics Register; Suicide registry
1973	Medical Birth Registry; Register of Legally Induced Abortions
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2014	Danish Colorectal Cancer Screening Database

SAMMENHÆNGE MELLEM BLODPROPPER I ØJET OG HJERTE-KAR-SYGDOMME

- Vores projekt

Overordnet plan

Del	Formål
I	Undersøge risikofaktorer for udvikling af arterielle blodpropper i øjet
II	Undersøge blodpropper i øjet som tidlig indikator for sygdomsudvikling

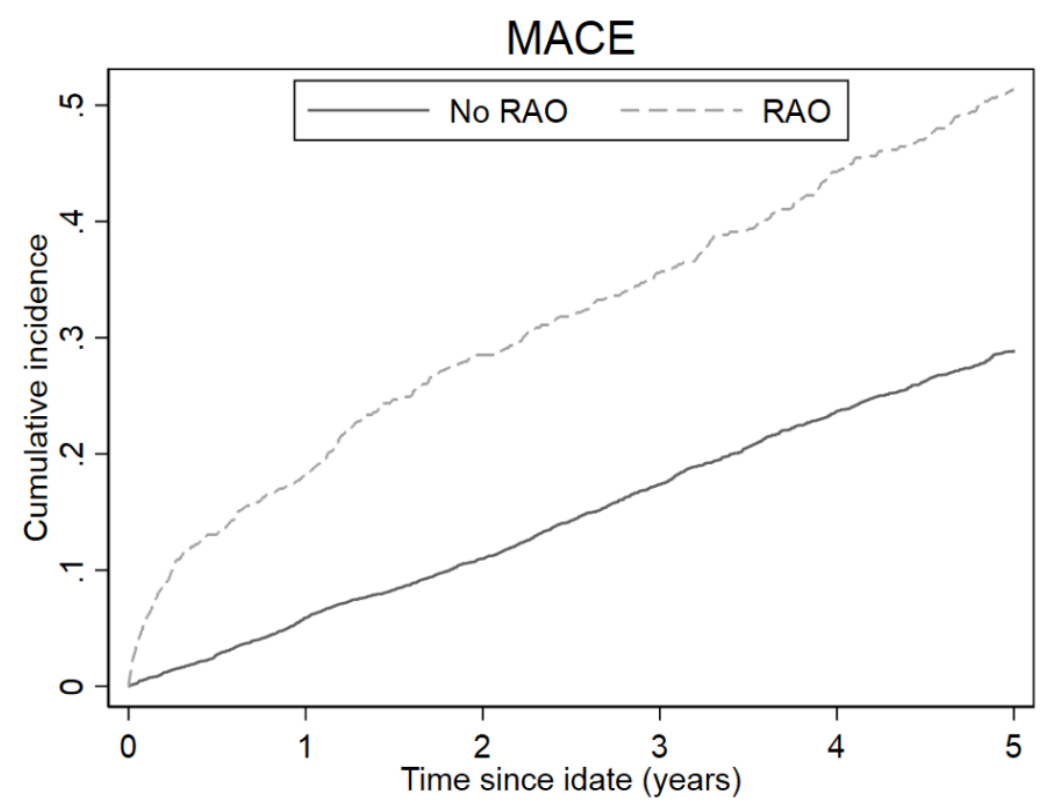
Planlagte studier – del 1

Studie	Formål	Design
1	Oversigtsstudie over risikofaktorer for RAO	Case-control studie RAO cases Raske kontroller
2	Undersøge hvorvidt RAO og apopleksi er ækvivalente sygdomme	Case-control studie RAO cases Apopleksi kontroller
3	Undersøge om RAO og RVO er samme sygdom med forskellige kliniske præsentationer	Case-control studie RAO cases RVO kontroller

Planlagte studier – Del 2

Studie	Formål	Design
4	Vurdere RAO som prædiktor for komplikationer i diabetes patienter	Kohorte studie Diabetiske RAO patienter Diabetes kontroller uden RAO
5	Evaluere brugen af apopleksi risiko scorer som arbejdsredskab i vurderingen af RAO patienters risiko for apopleksi	Kohorte studie RAO population

Kumuleret incidens



Tak til

REGION NORDJYLLAND
– i gode hænder

Synoptik Fonden

Bagger-Sørensen Fonden

Øjenforeningen

Svend Andersen Fonden

DET OBELSKE FAMILIEFOND

Herta Christensens Fond

Speciallæge Heinrich Kopps legat

AALBORG UNIVERSITET

THE VELUX FOUNDATIONS
VILLUM FONDEN VELUX FONDEN

Tak til:

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Aalborg Universitetshospital:
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Toke Bek, Professor, ledende overlæge, dr.med.
Jesper Hjortdal, Professor, overlæge, dr.med., ph.d.
Steen Fiil Urbak, Overlæge, ph.d.
Mikkel Funding, Afdelingslæge, ph.d.
Mikkel Lyngholm, Afdelingslæge, ph.d.

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Kirsten Peterslund, Laborant
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Morten Dornonville de la Cour, Professor, dr.med.
Michael Larsen, Professor, overlæge, dr.med.
Henrik Lund Andersen, professor, overlæge, dr.med.
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Nanna Vestergaard Azuz
Marie Ørskov
Malene Krog
Gabriele Byskov
Danson Mutuvele
Marie Skallerup Andersen

Tak til:

<u>Familie</u>:

Mette og Emma

Et godt syn til alle - hele livet

Tak er kun et fattigt ord!