Selvita

Improving nonclinical research practices: Way forward 2022

LAS webinar series organized by CroLASA in collaboration with SLAS

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Role of pathology in biomedical research

Snježana Čužić, PhD, MD, Pathologist

May 2022

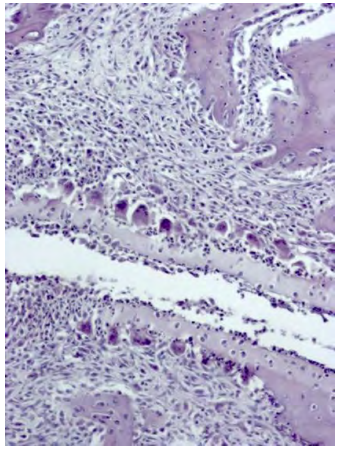
Aim of the lecture

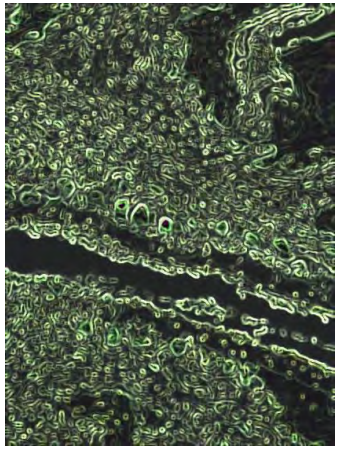
Present the role of pathology in drug research conducted on:

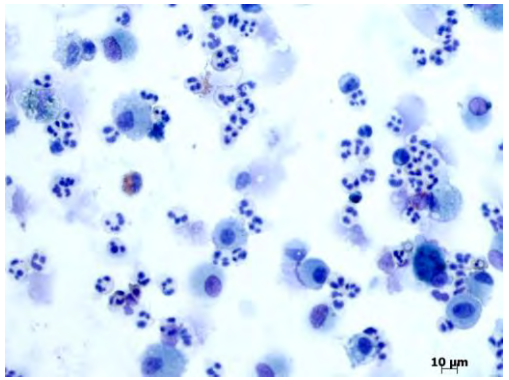
Laboratory animals

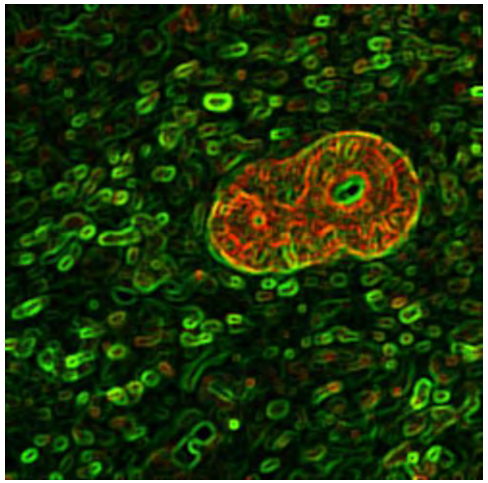
Human tissue samples

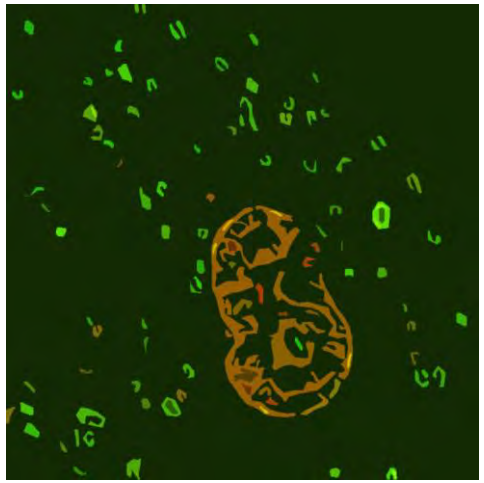
Tissue/cell lines grown *in vitro*

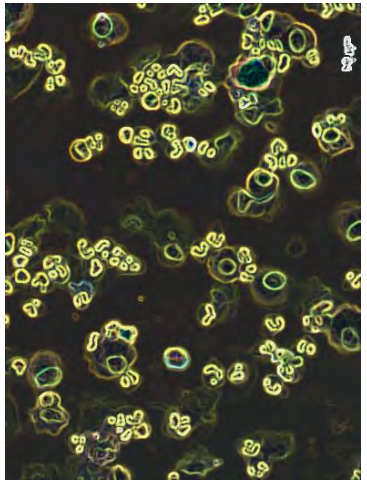


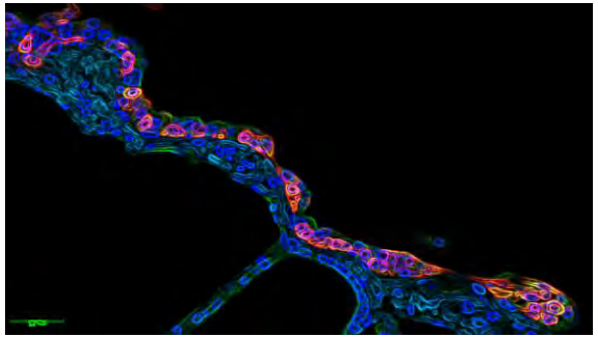


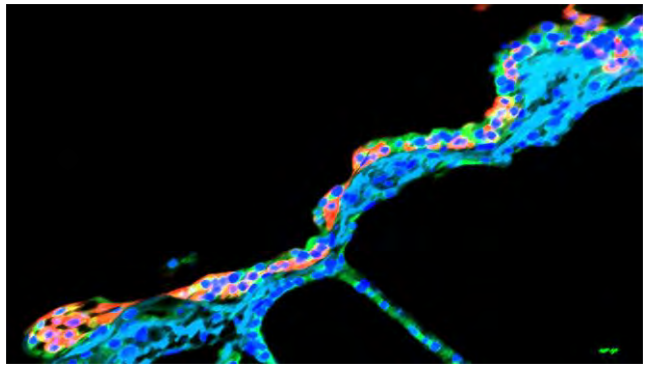


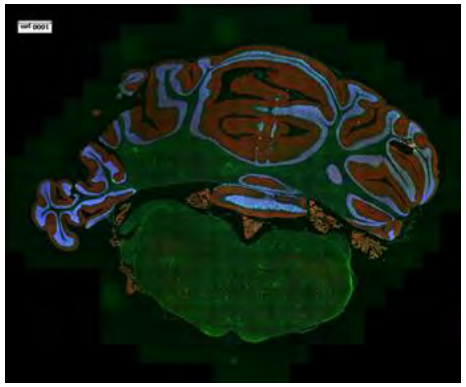


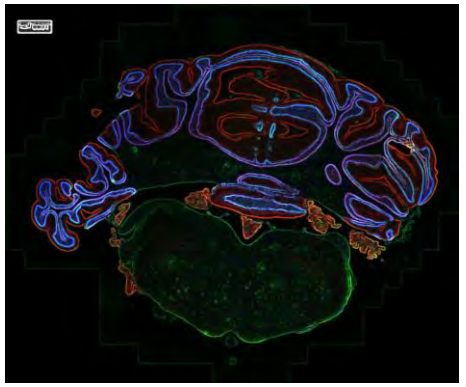


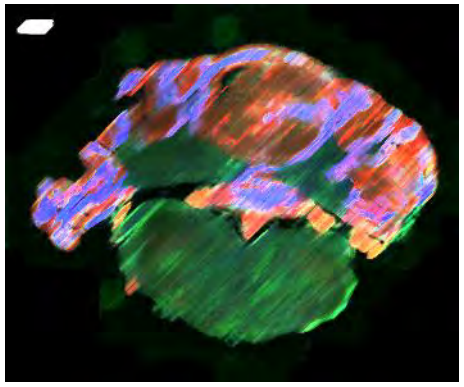






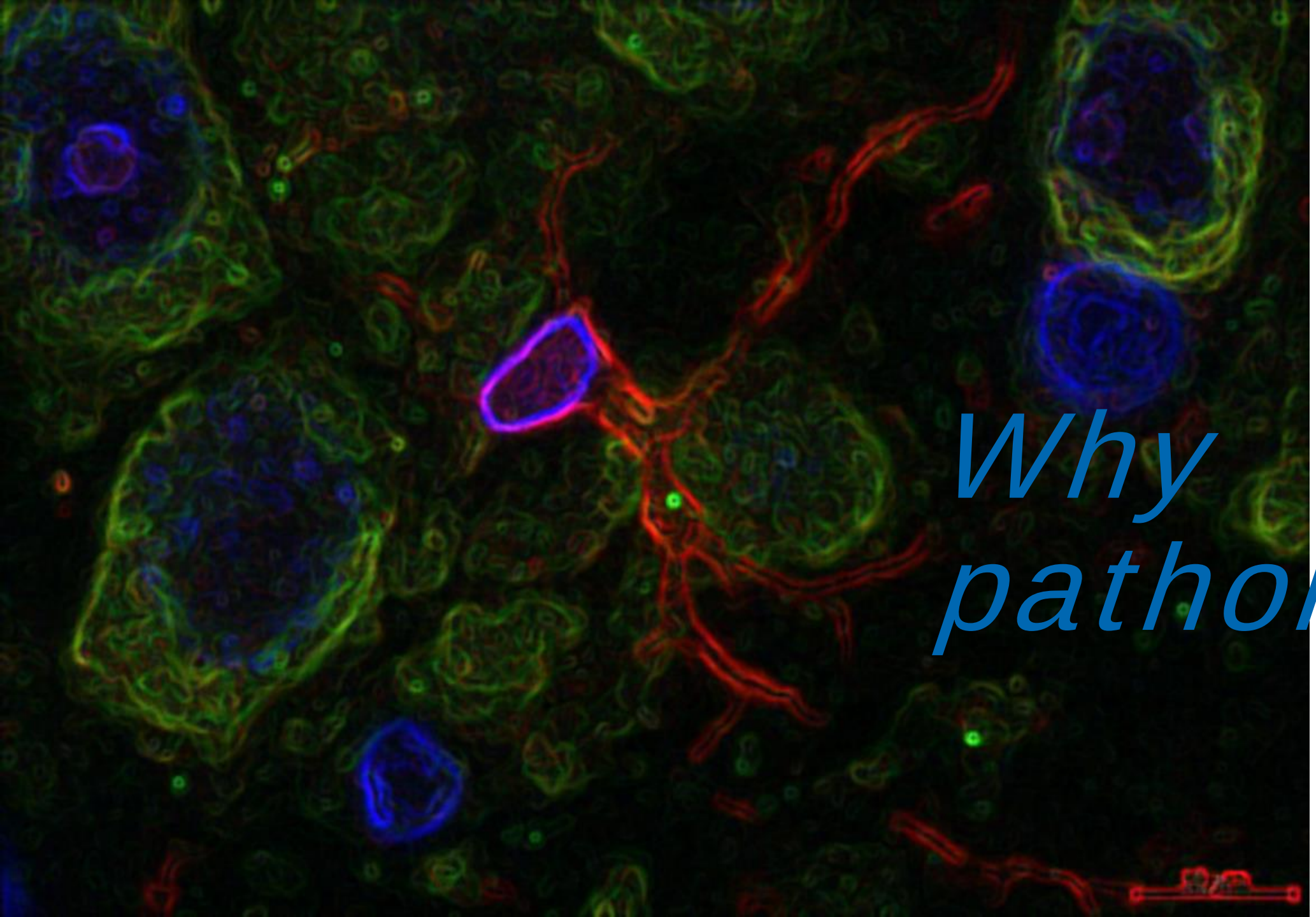






What has changed?


Reduce late-phase attrition
Translational medicine
Pathobiology
Comparative medicine
Translational biomarkers
Comparative medicine veterinarians
Pathologist
Translational relevance
Pathology
Data integration
Data integrity
Data quality
Translational pathology
Comparative pathobiology



Why pathology?

Pathology in biomedical research: From target to clinical trials

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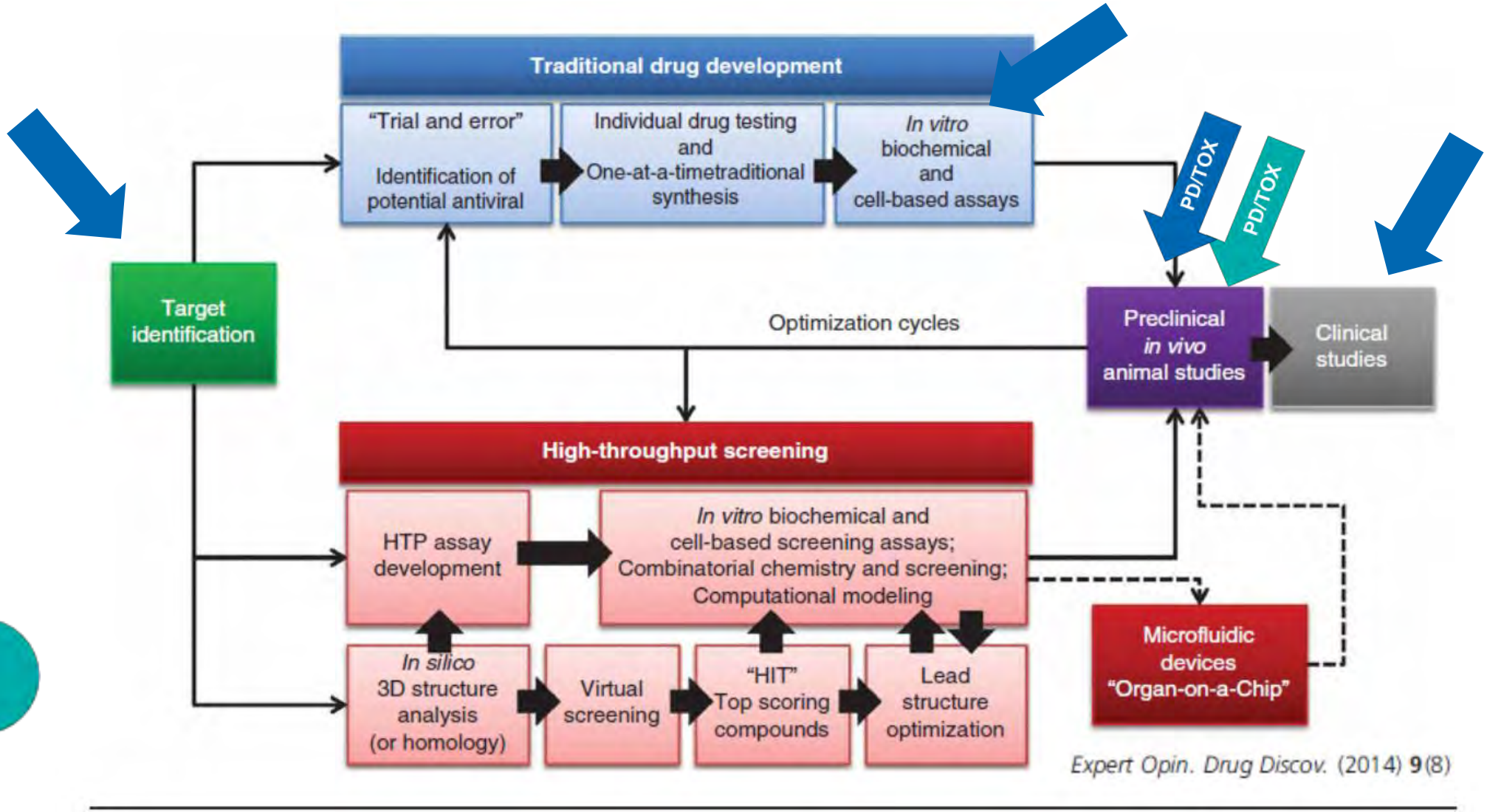
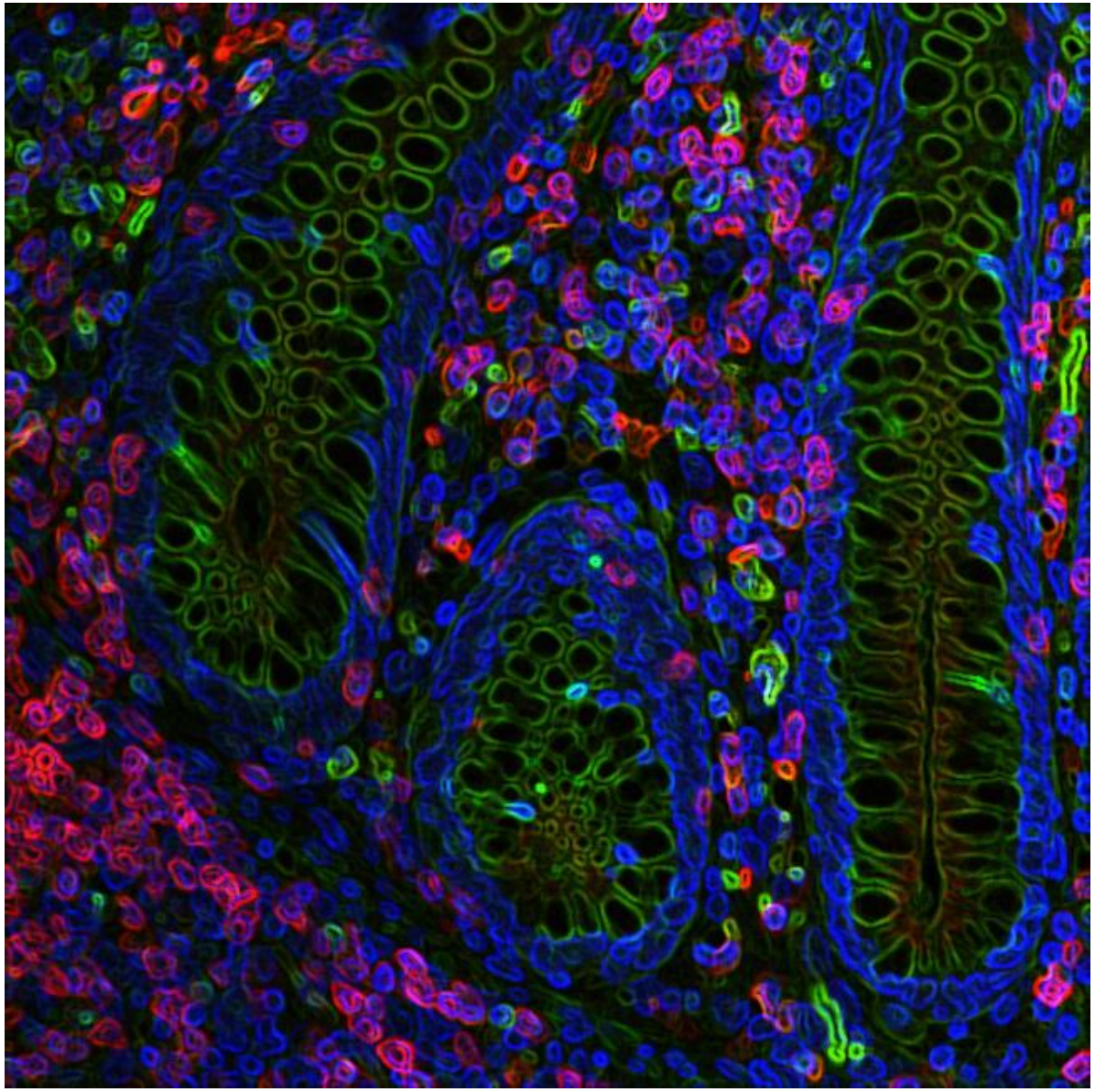
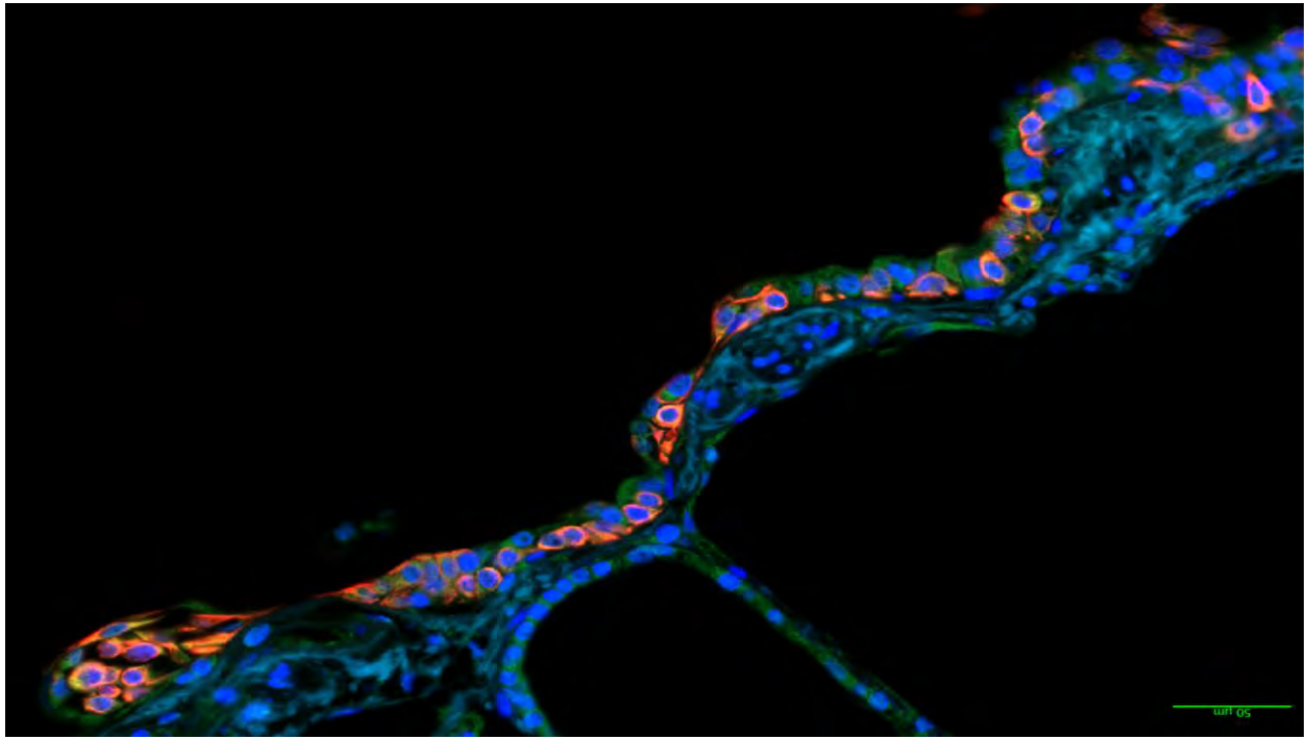


Expert Opin. Drug Discov. (2014) **9**(8)

Target /Pathway validation



In vivo, In vitro



Target validation: Human disease

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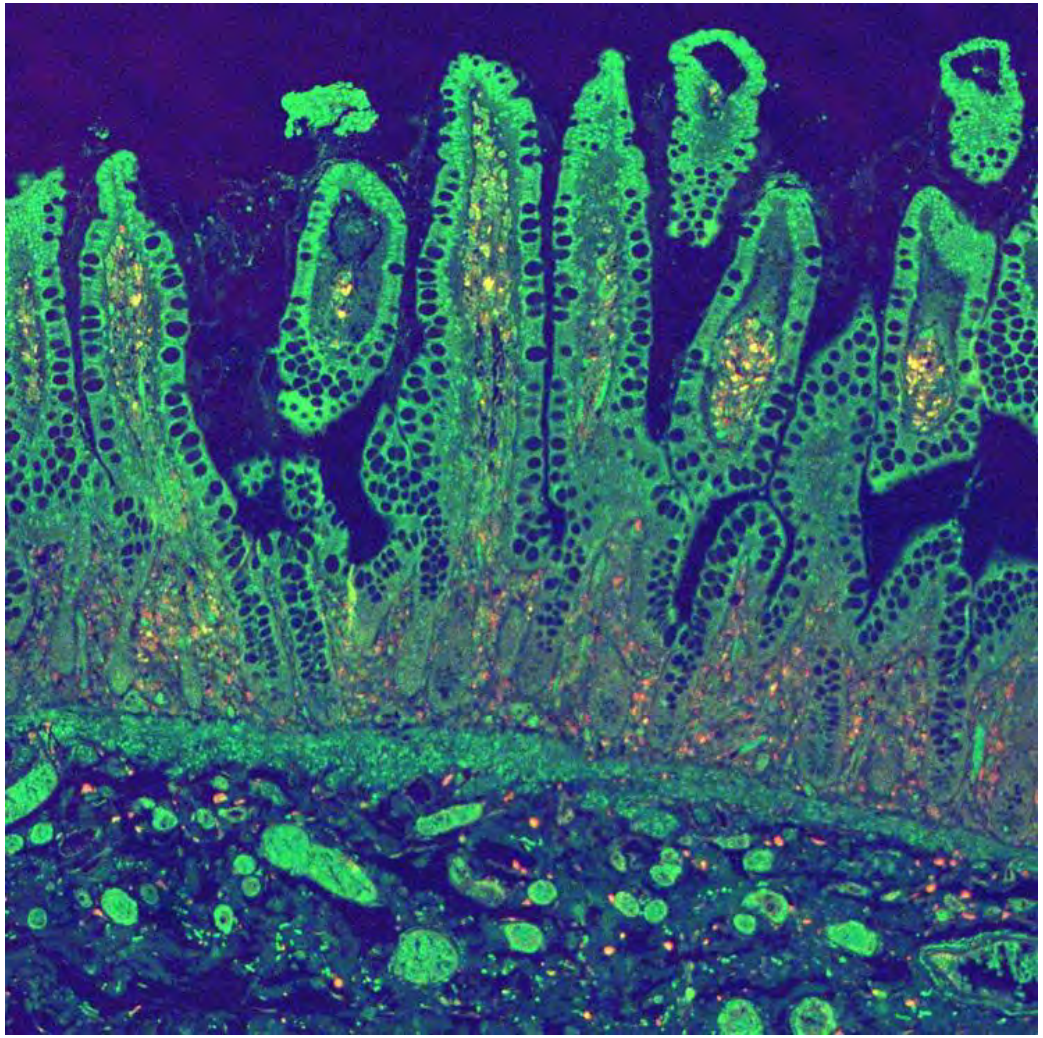
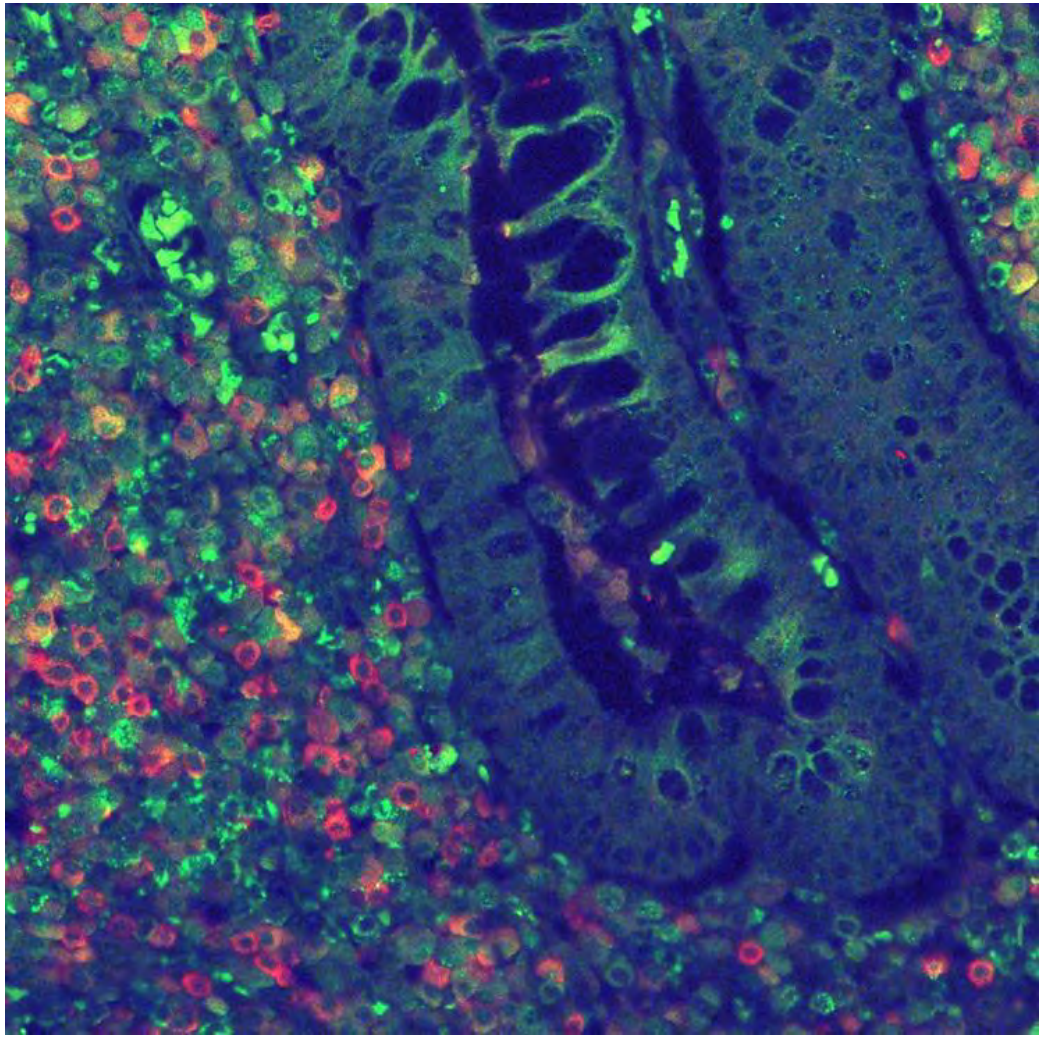
Human, non-IBD



TargetCD-marker

Human, IBD



TargetCD-marker

Target validation: Translational pathology
Human vs. animal tissue

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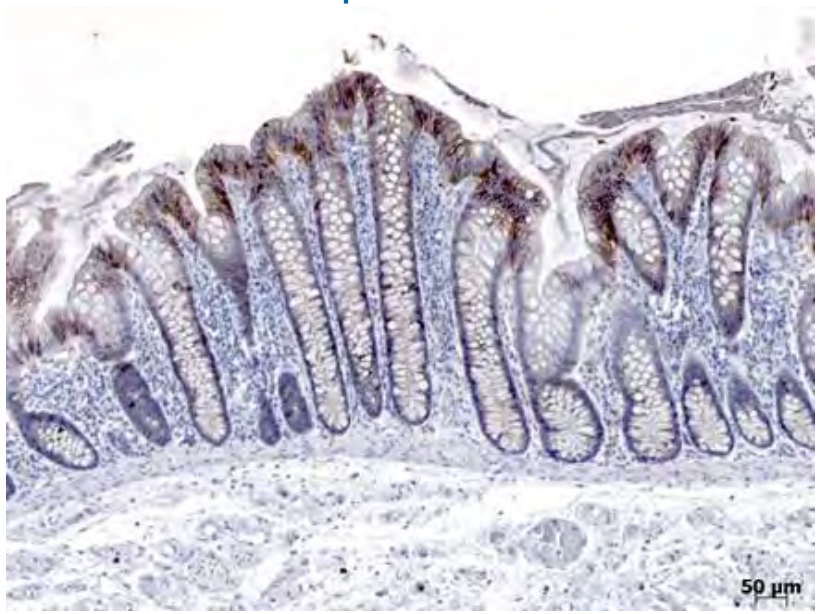
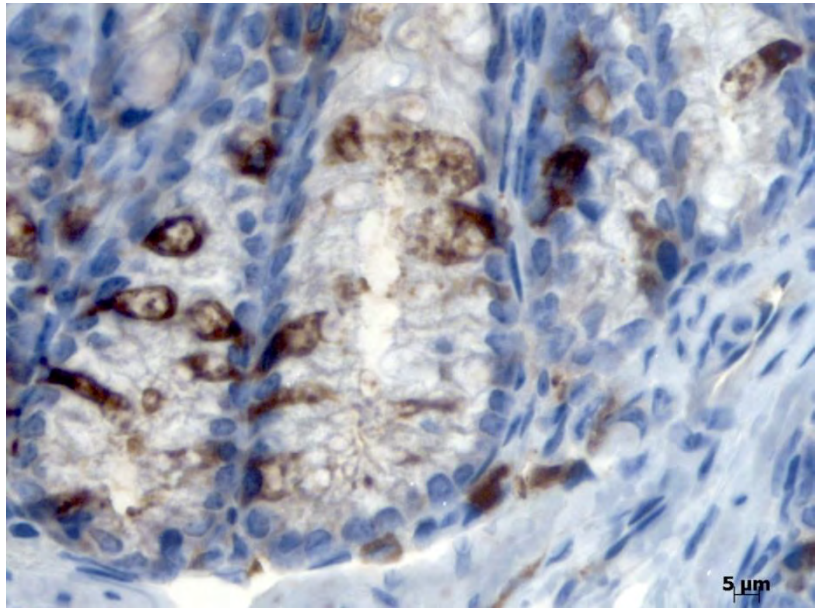
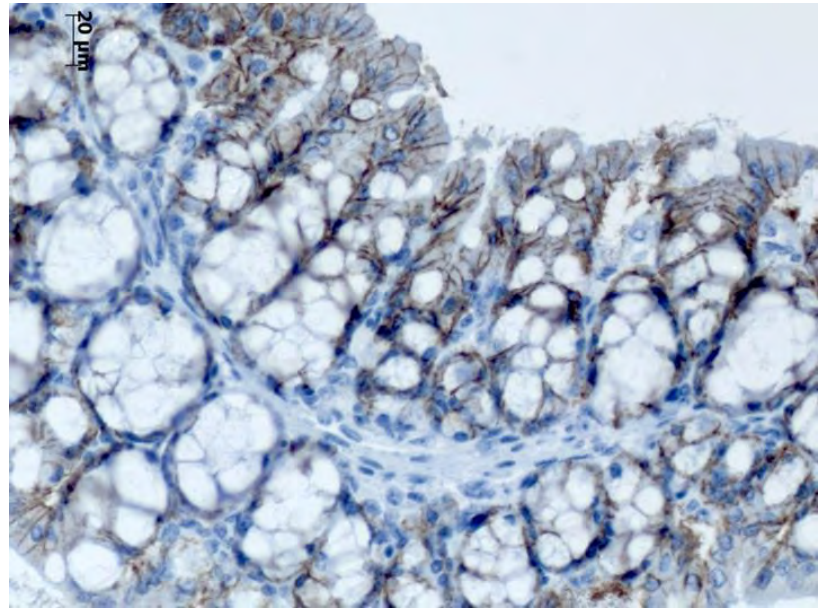
Claudin-1 expression in colon







Homo sapiens

C57Bl/6

SCID

frontiers in Pharmacology

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Claudins: Beyond Tight Junctions in Human IBD and Murine Models

OPEN ACCESS

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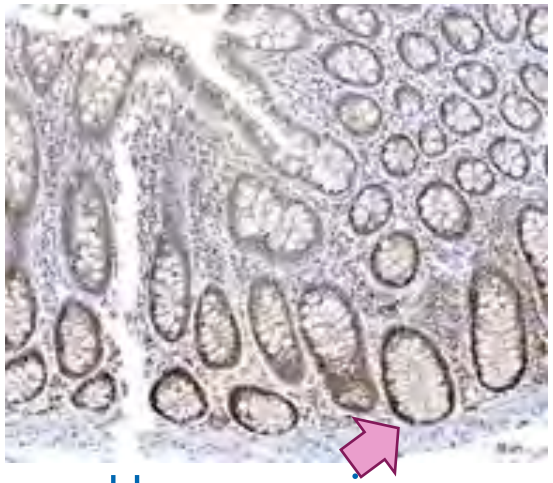
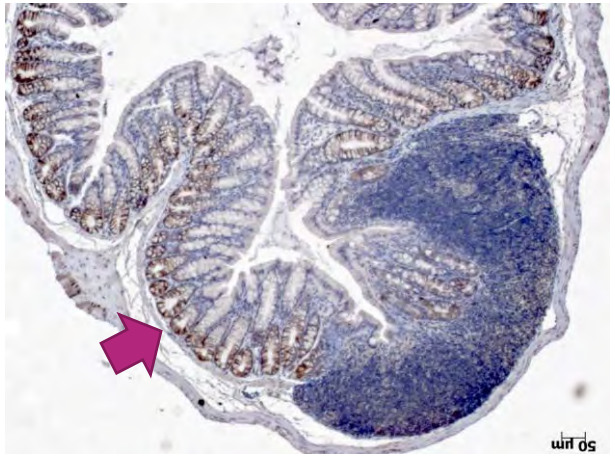
Target validation: Translational pathology

Human vs. animal models

Claudin-2 expression in colon



Homo sapiens



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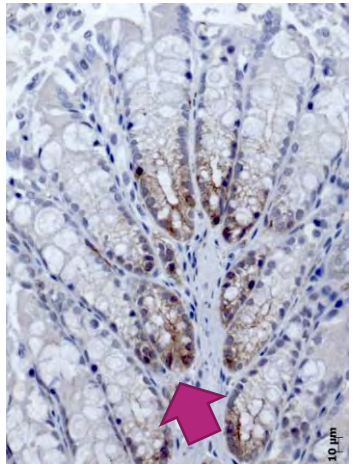

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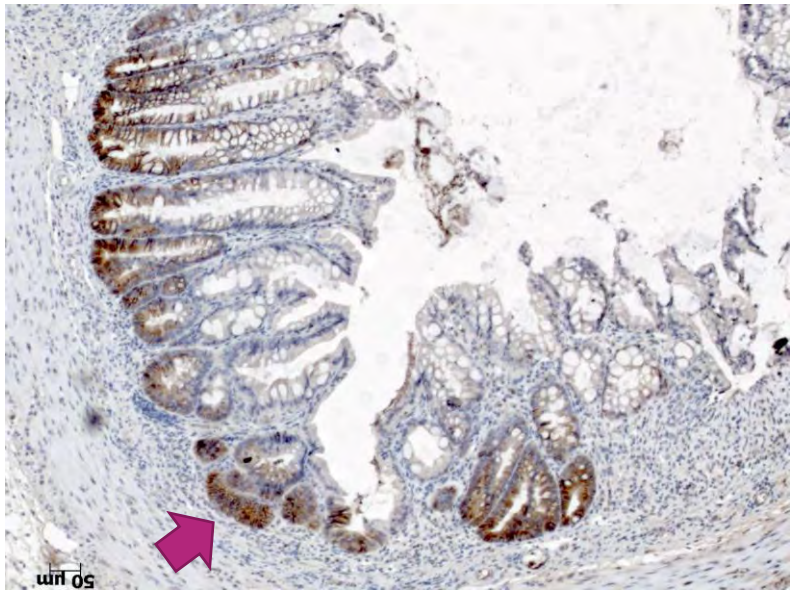
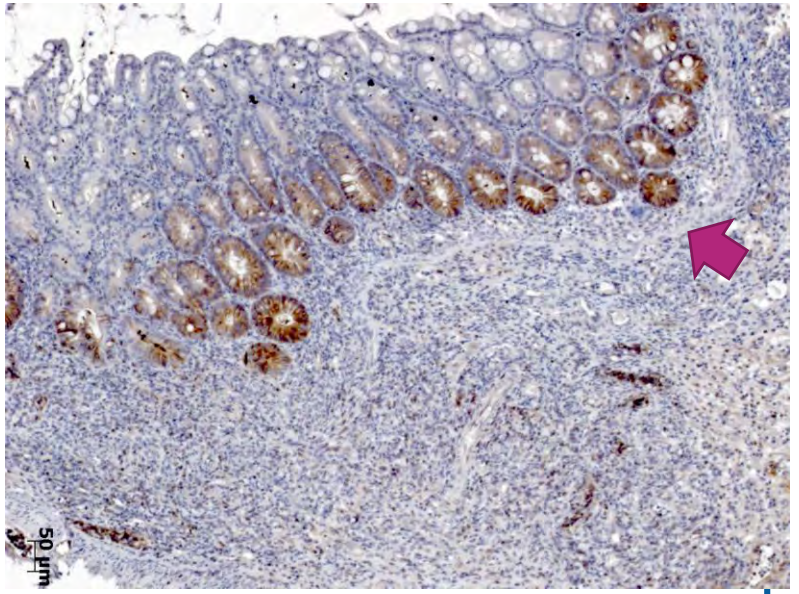
IBD



DSS



Adoptive transfer

Target validation: Human vs. *in vitro* ***models***

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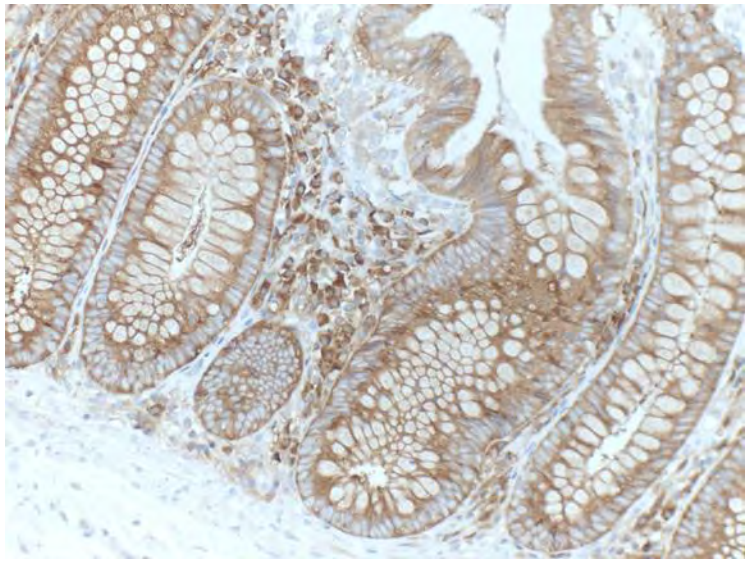
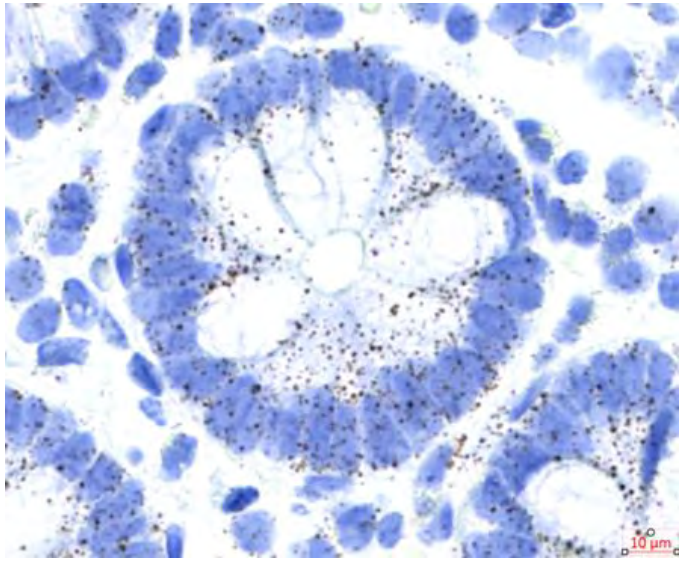
Target expression in human colon; IHC/ISH

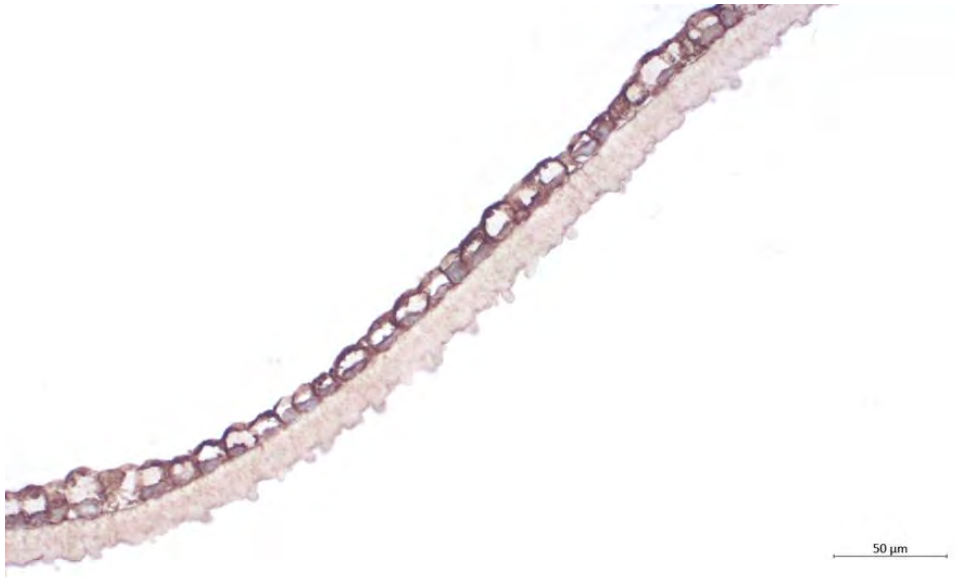


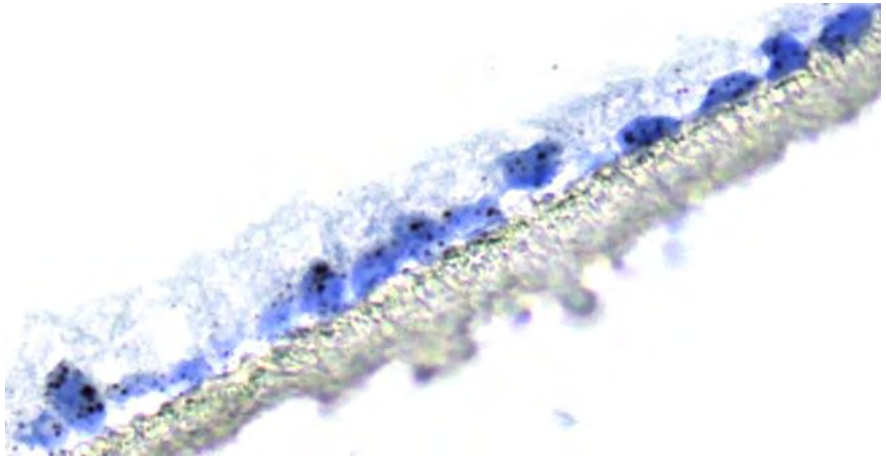
Protein,IHC



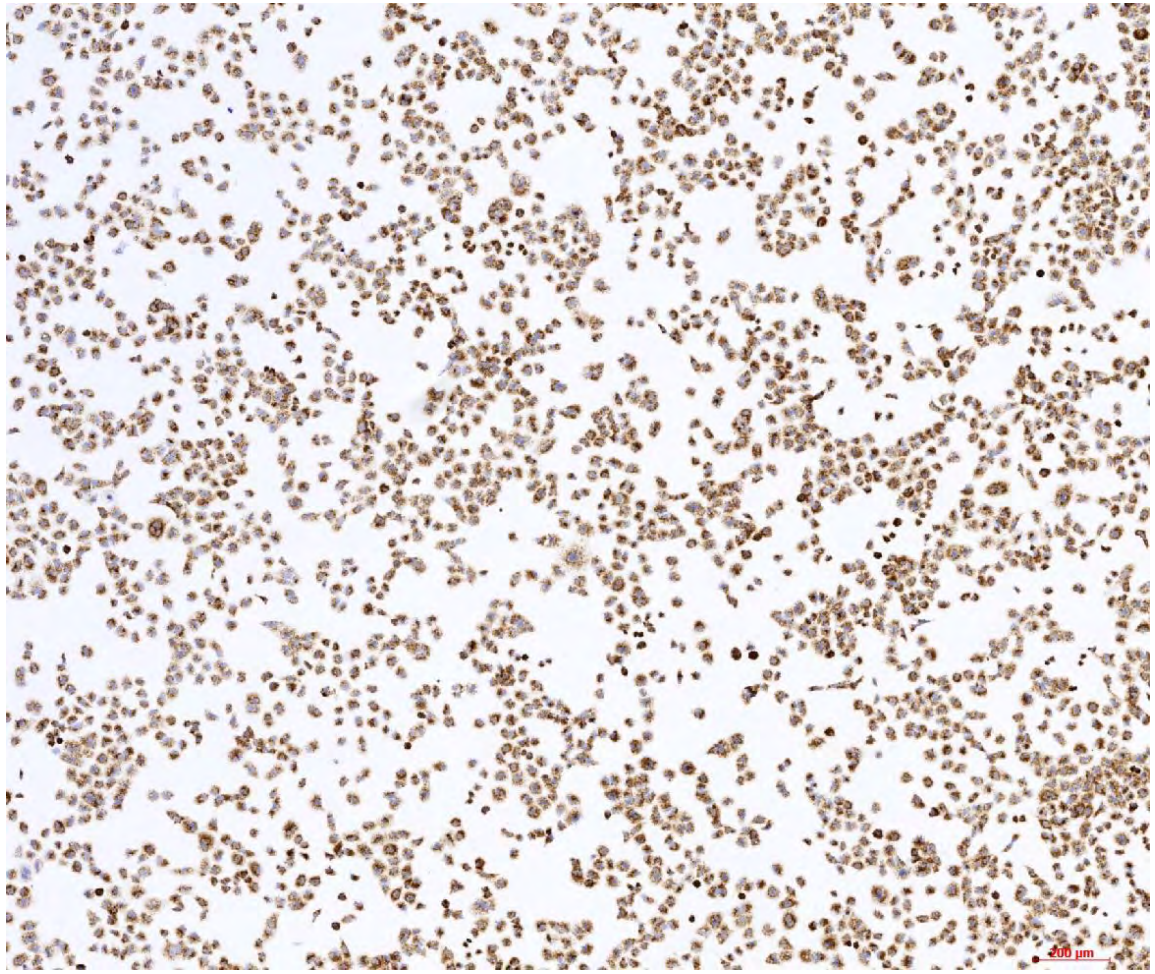
mRNA, ISH

Target expression in Caco2 cell line; IHC/ISH

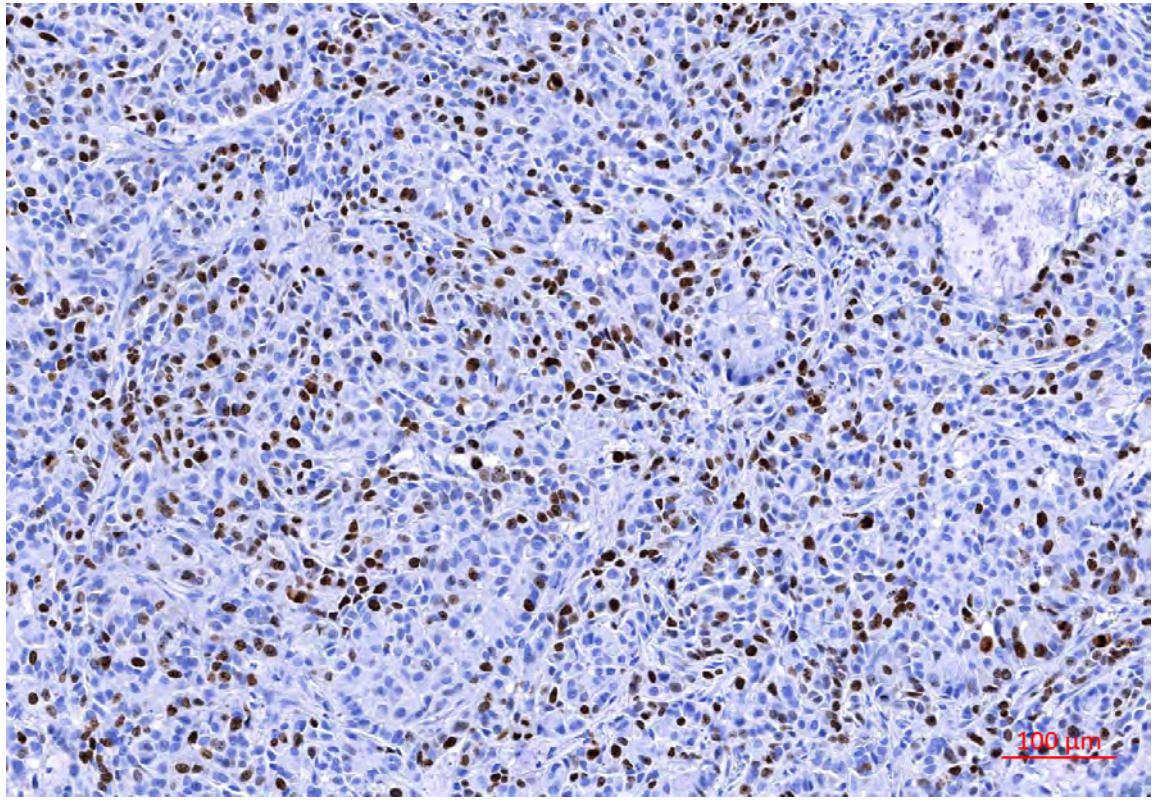




Target validation: *in vitro* ***vs.*** *in vivo* ***models***



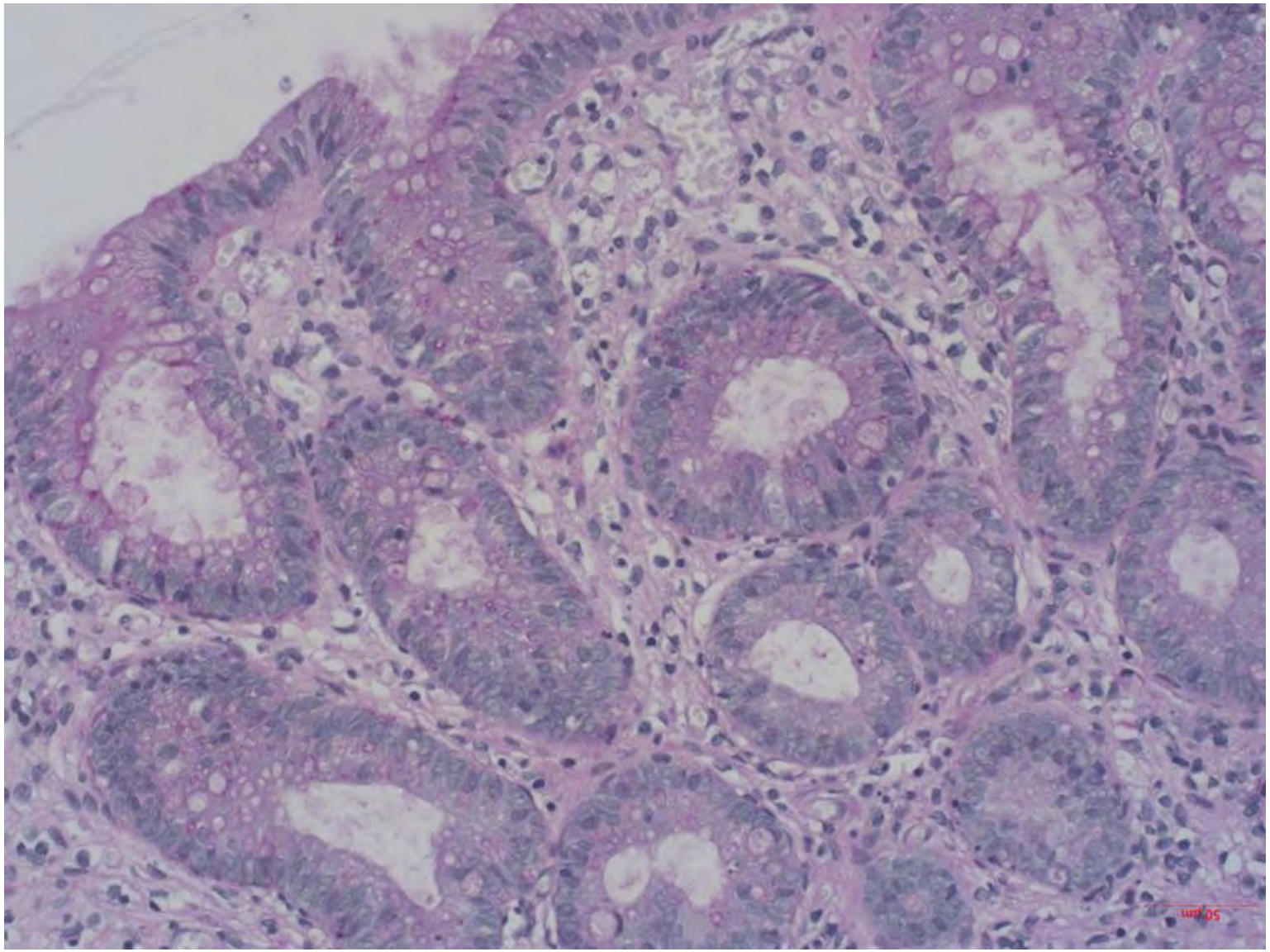
A549 cell-line grown on a slide, mRNA, ISH



A549 xenograft, protein,IHC

In vitro assays

Are results gained in *in vitro* assay affected by tissue alterations?



IBD, Colon biopsy at D1 in culture

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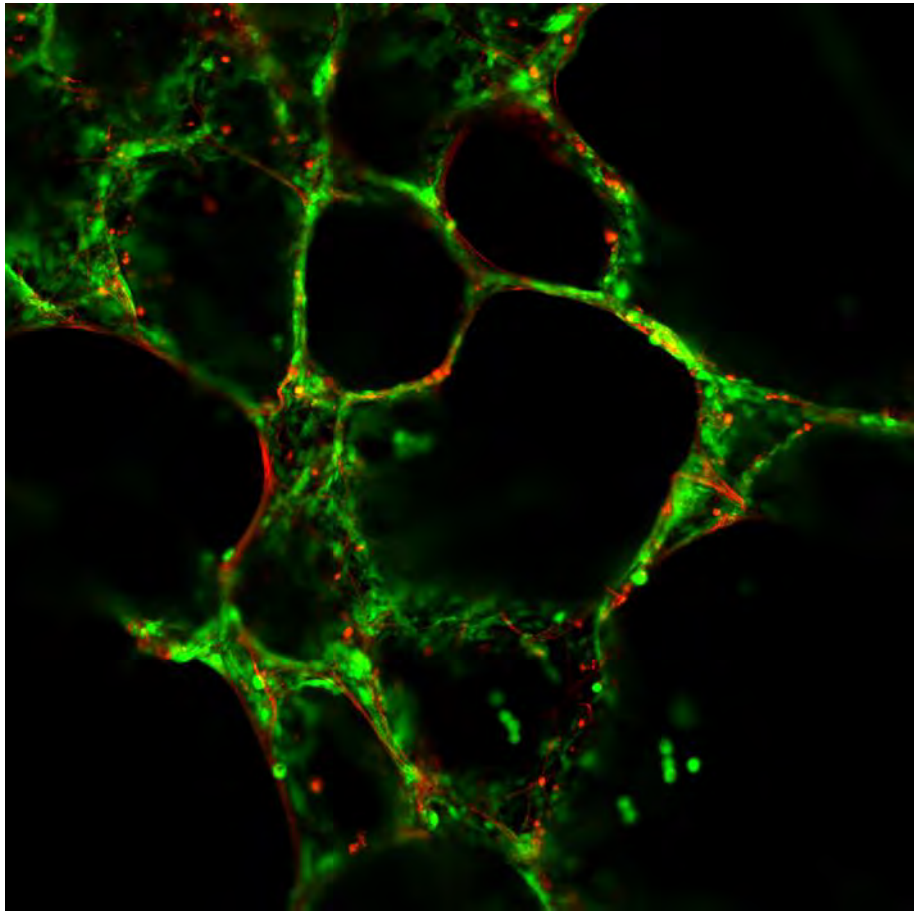
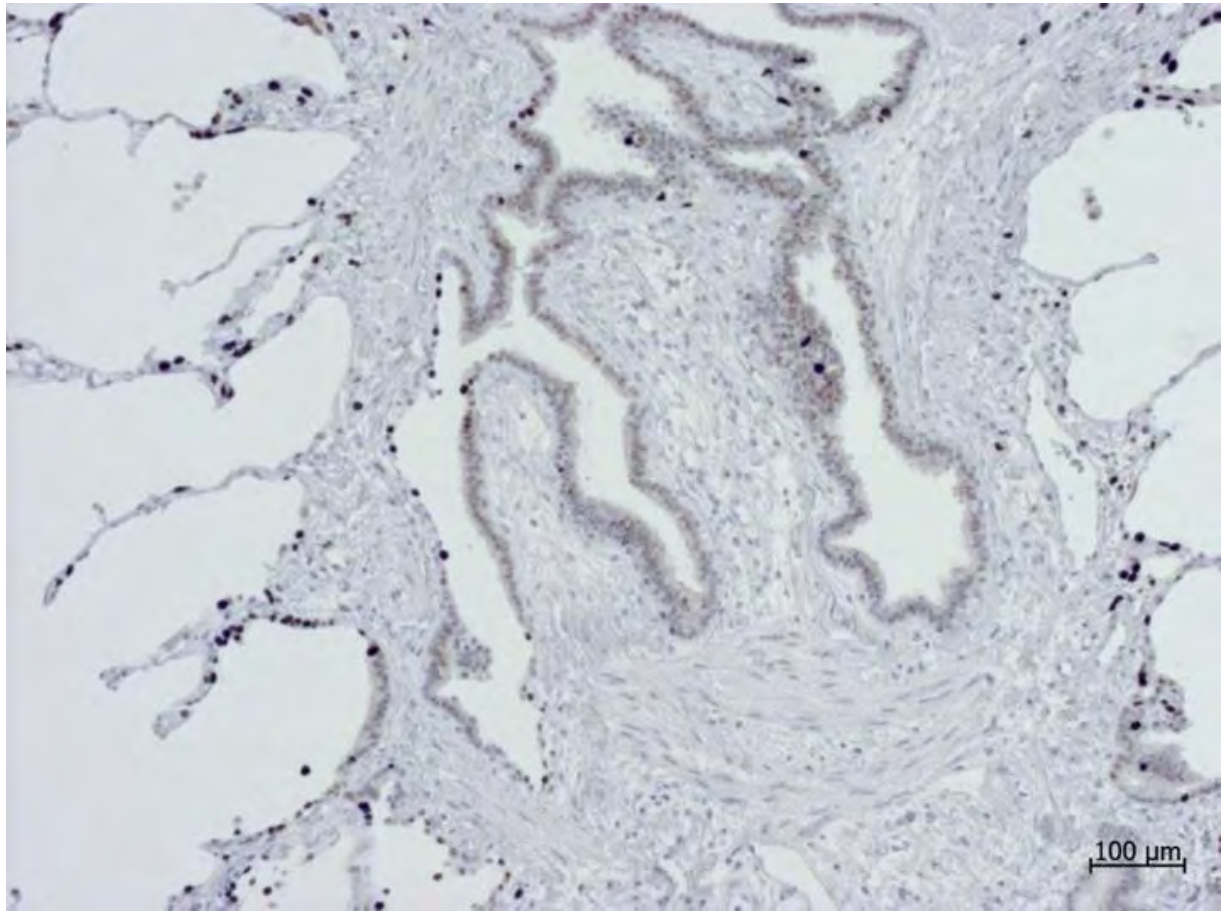
COPD, Precision cut human lung slices at D3 in culture



Propidium iodide **SYTO9**



Ki67

Animal studies

Bleomycin induced lung fibrosis; CO1A1 IHC

Animal model: Target(s) validation

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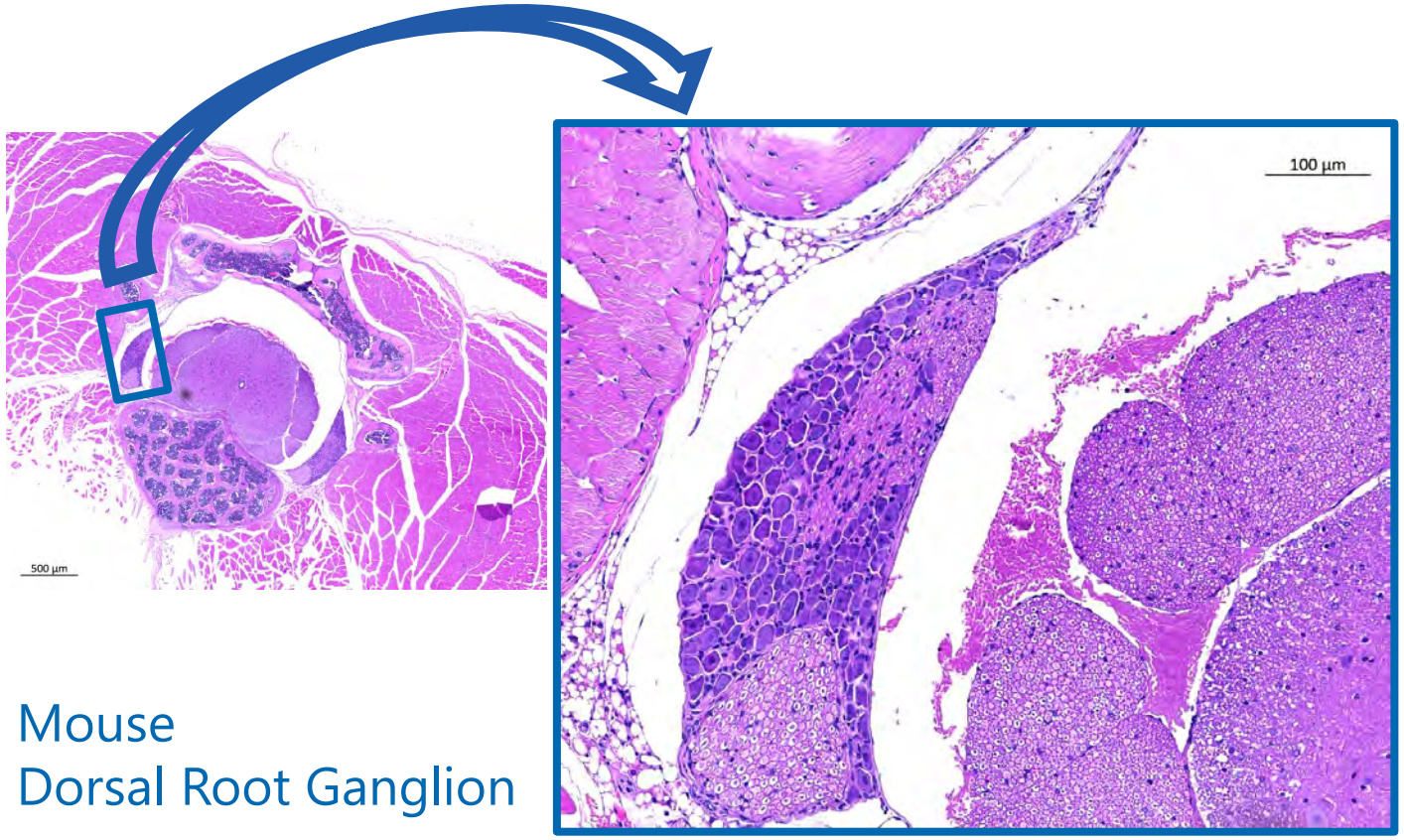
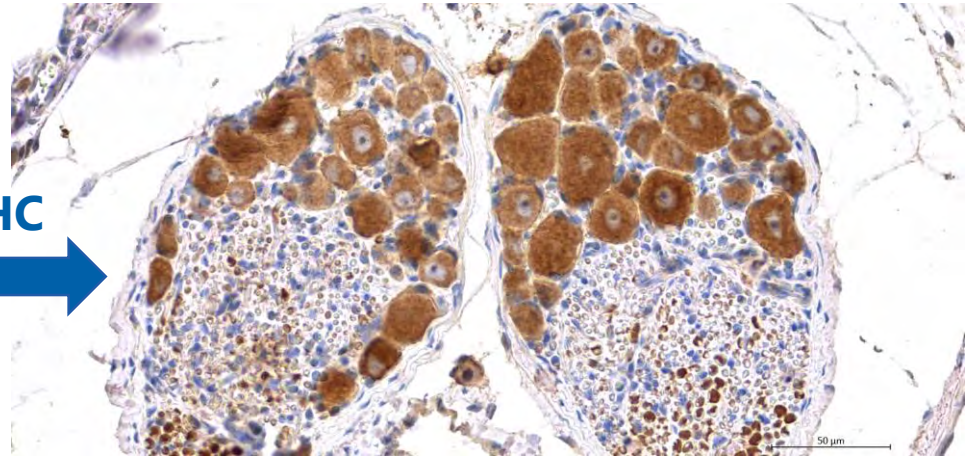
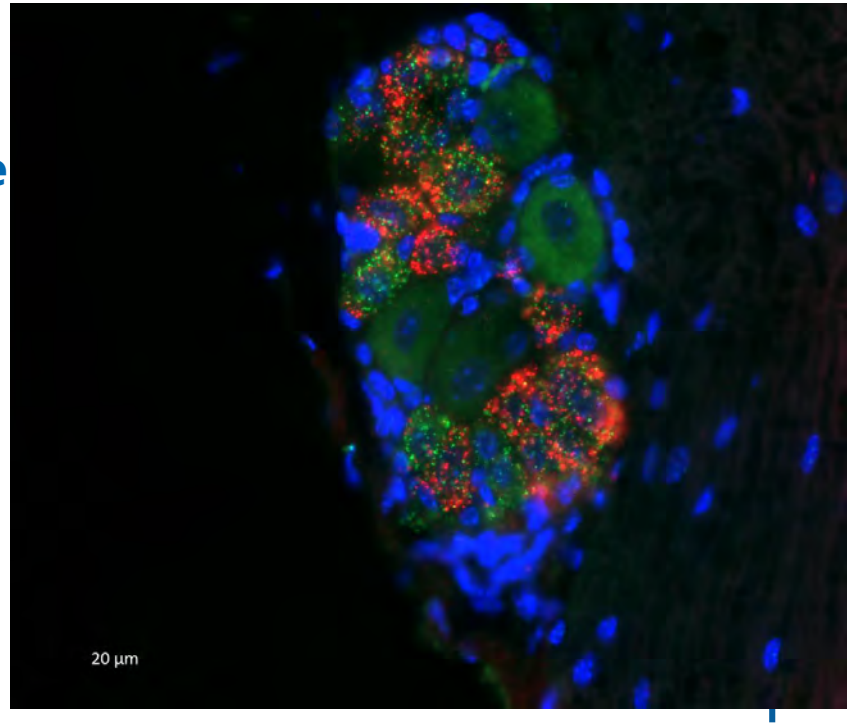


Mouse
Dorsal Root Ganglion

IHC



Double ISH



Animal model: Pathophysiology

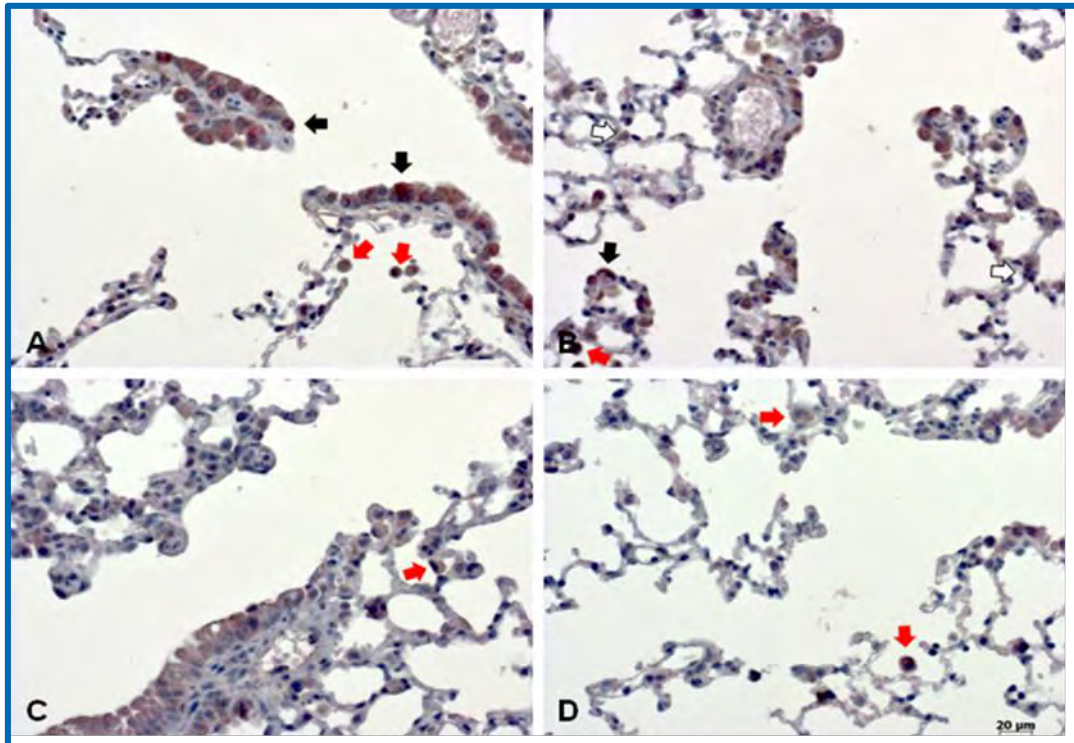
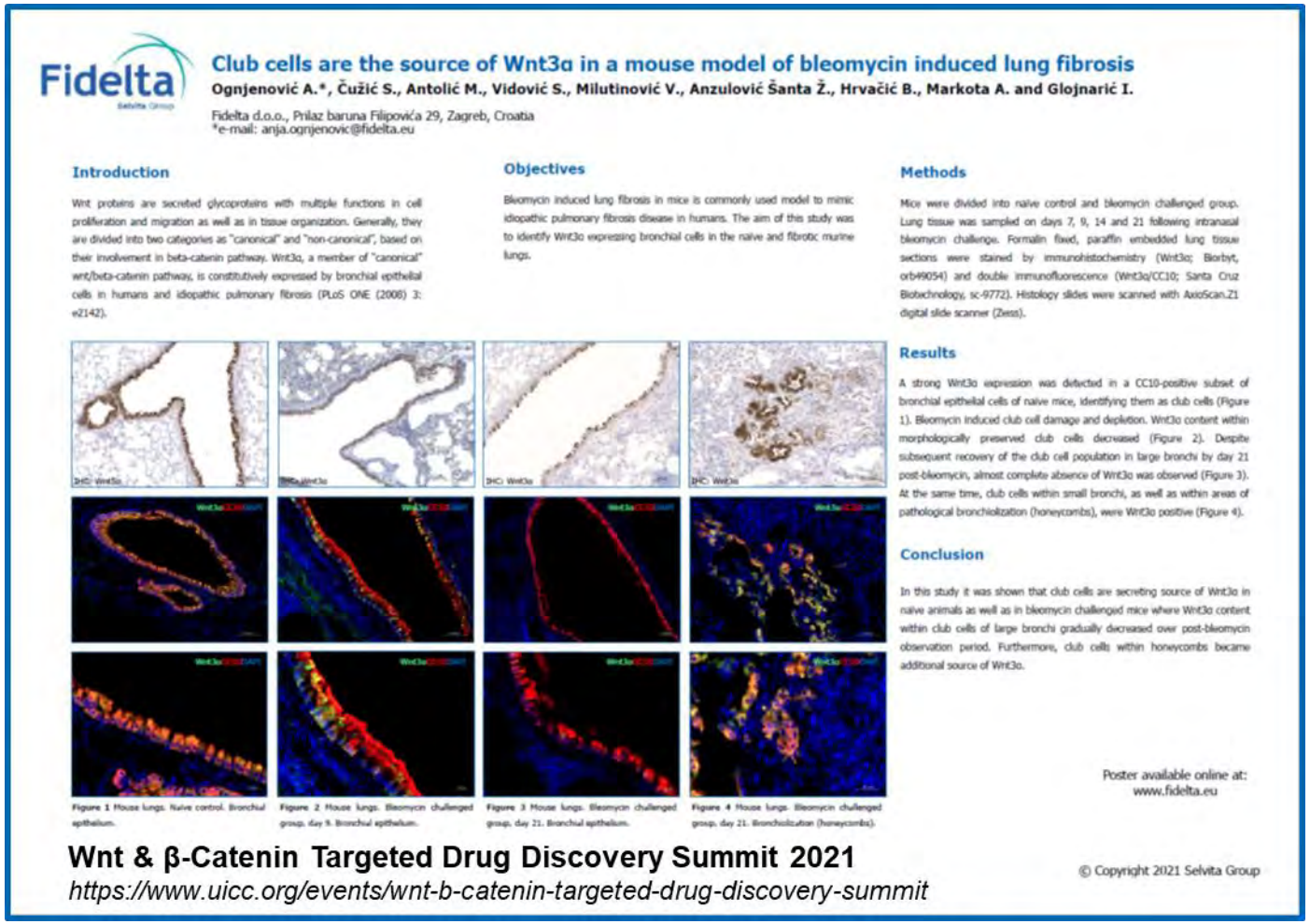


FIGURE 19.—Nitrotyrosine in sham exposed lungs (A) and after smoke exposure (B-D). Nitrotyrosine in sham exposed lungs (A) was present in the cytoplasm of alveolar macrophages (red arrow) and Clara cells (blue arrow). One day after exposure to smoke from 3 x 2 cigarettes for 2 consecutive days, cells lining alveolar ducts (black arrow) (B) and AEC-II (white arrow) (C) stained positive. Alveolar macrophage staining increased in comparison to that in sham-exposed lungs (red arrow) (C). At day 7 postexposure (D), only alveolar macrophages (red arrow) stained with variable intensity.

Čužić *et al*. Toxicologic Pathology, 00: 1-19, 2012



Fidelta

Club cells are the source of Wnt3α in a mouse model of bleomycin induced lung fibrosis

Ognjenović A.*, Čužić S., Antolić M., Vidović S., Milutinović V., Anzulović Šanta Ž., Hrvačić B., Markota A. and Glojnarić I.

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Introduction

Wnt proteins are secreted glycoproteins with multiple functions in cell proliferation and migration as well as in tissue organization. Generally, they are divided into two categories as "canonical" and "non-canonical", based on their involvement in beta-catenin pathway. Wnt3α, a member of "canonical" wnt/beta-catenin pathway, is constitutively expressed by bronchial epithelial cells in humans and idiopathic pulmonary fibrosis (PLoS ONE (2008) 3: e2142).

Objectives

Bleomycin induced lung fibrosis in mice is commonly used model to mimic idiopathic pulmonary fibrosis disease in humans. The aim of this study was to identify Wnt3α expressing bronchial cells in the naive and fibrotic murine lungs.

Methods

Mice were divided into naive control and bleomycin challenged group. Lung tissue was sampled on days 7, 9, 14 and 21 following intranasal bleomycin challenge. Formalin fixed, paraffin embedded lung tissue sections were stained by immunohistochemistry (Wnt3α; Biorbyt, orb49054) and double immunofluorescence (Wnt3α/CC10; Santa Cruz Biotechnology, sc-9772). Histology slides were scanned with AxioScan.Z1 digital slide scanner (Zeiss).

Results

A strong Wnt3α expression was detected in a CC10-positive subset of bronchial epithelial cells of naive mice, identifying them as club cells (Figure 1). Bleomycin induced club cell damage and depletion. Wnt3α content within morphologically preserved club cells decreased (Figure 2). Despite subsequent recovery of the club cell population in large bronchi by day 21 post-bleomycin, almost complete absence of Wnt3α was observed (Figure 3). At the same time, club cells within small bronchi, as well as within areas of pathological bronchiolization (honeycombs), were Wnt3α positive (Figure 4).

Conclusion

In this study it was shown that club cells are secreting source of Wnt3α in naive animals as well as in bleomycin challenged mice where Wnt3α content within club cells of large bronchi gradually decreased over post-bleomycin observation period. Furthermore, club cells within honeycombs became additional source of Wnt3α.

Poster available online at:
www.fidelta.eu

Wnt & β-Catenin Targeted Drug Discovery Summit 2021
https://www.uicc.org/events/wnt-b-catenin-targeted-drug-discovery-summit

Animal model: Pathophysiology

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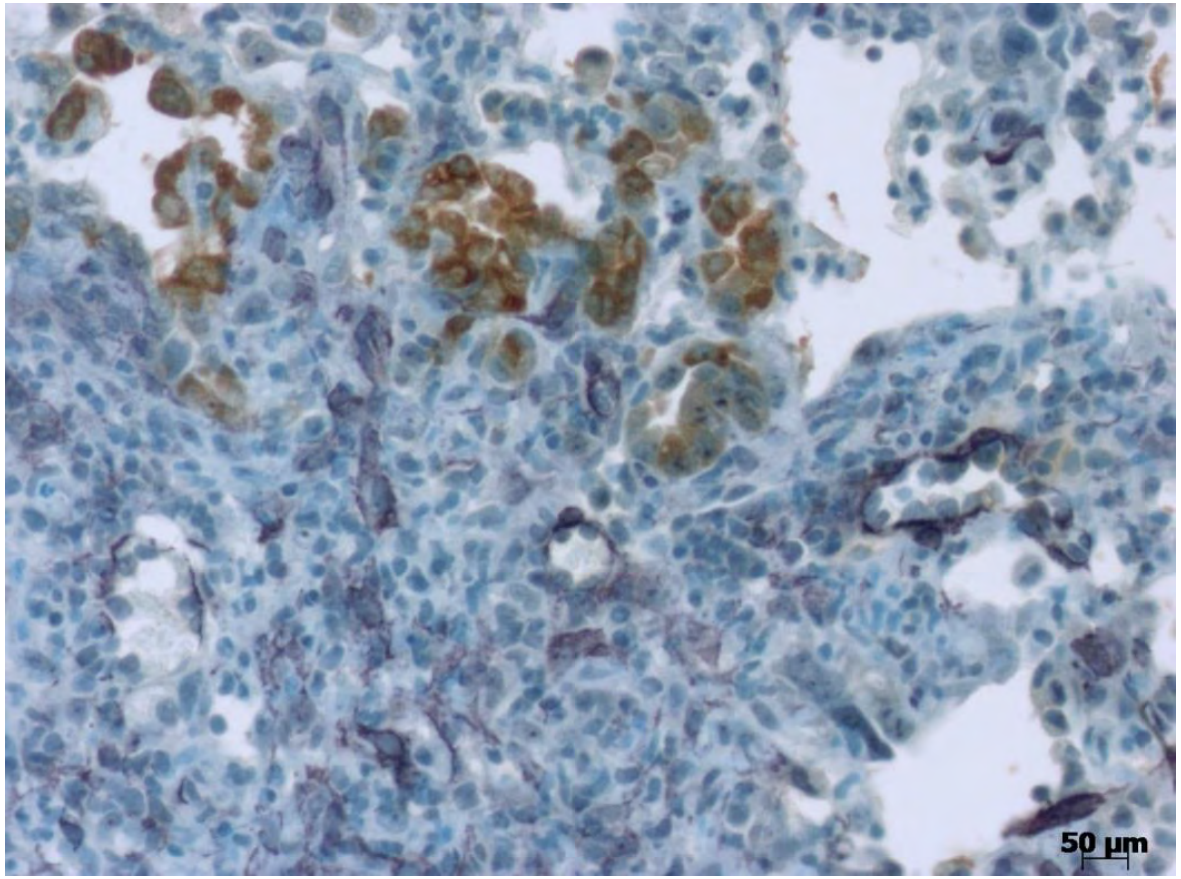
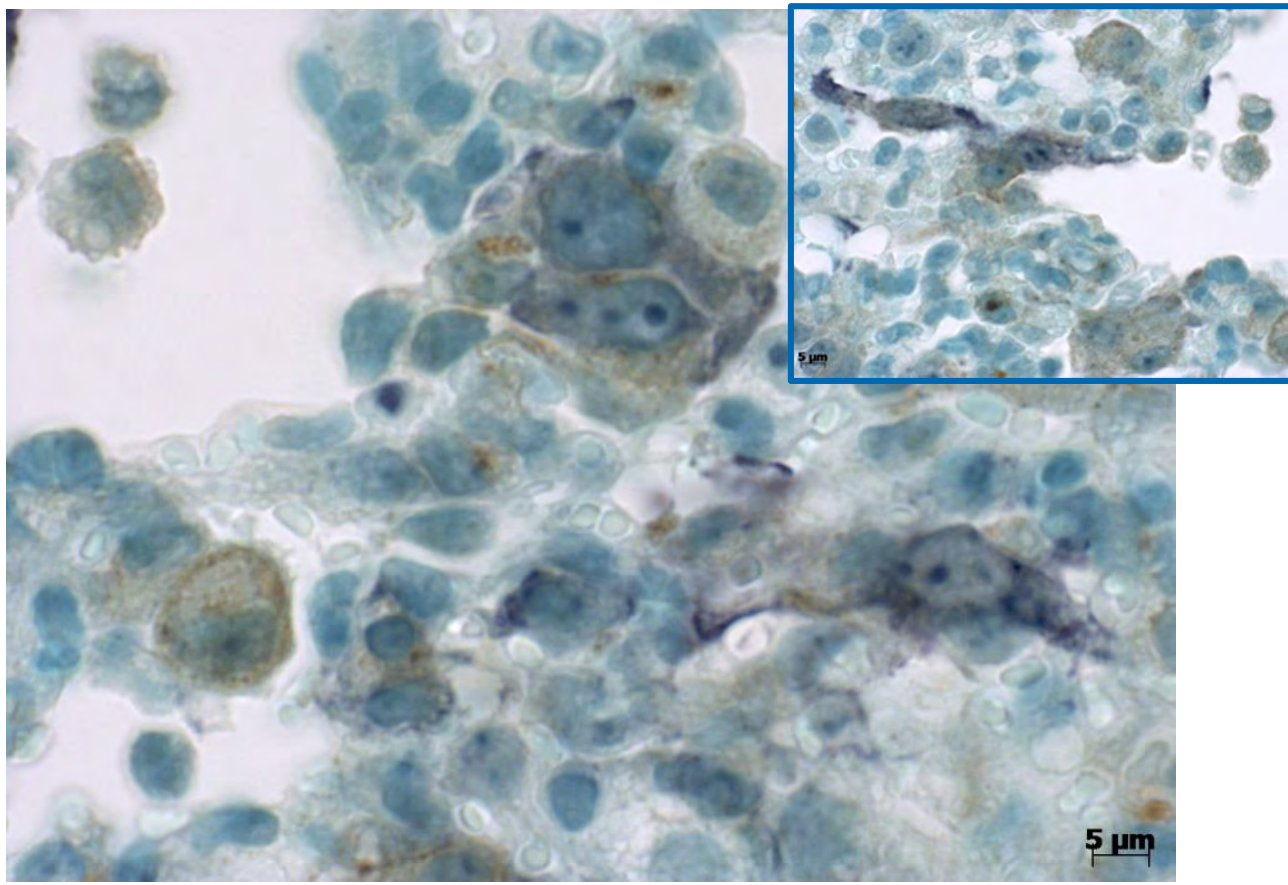
Bleomycin induced pulmonary fibrosis, *Pathological cell trans-differentiation*



Club cells and myofibroblasts
Uteroglobin/CC10 aSMA



Epithelial-mesenchymal transition (EMT)
Integrin aV aSMA

Animal model: Pathophysiology beyond "target" organ

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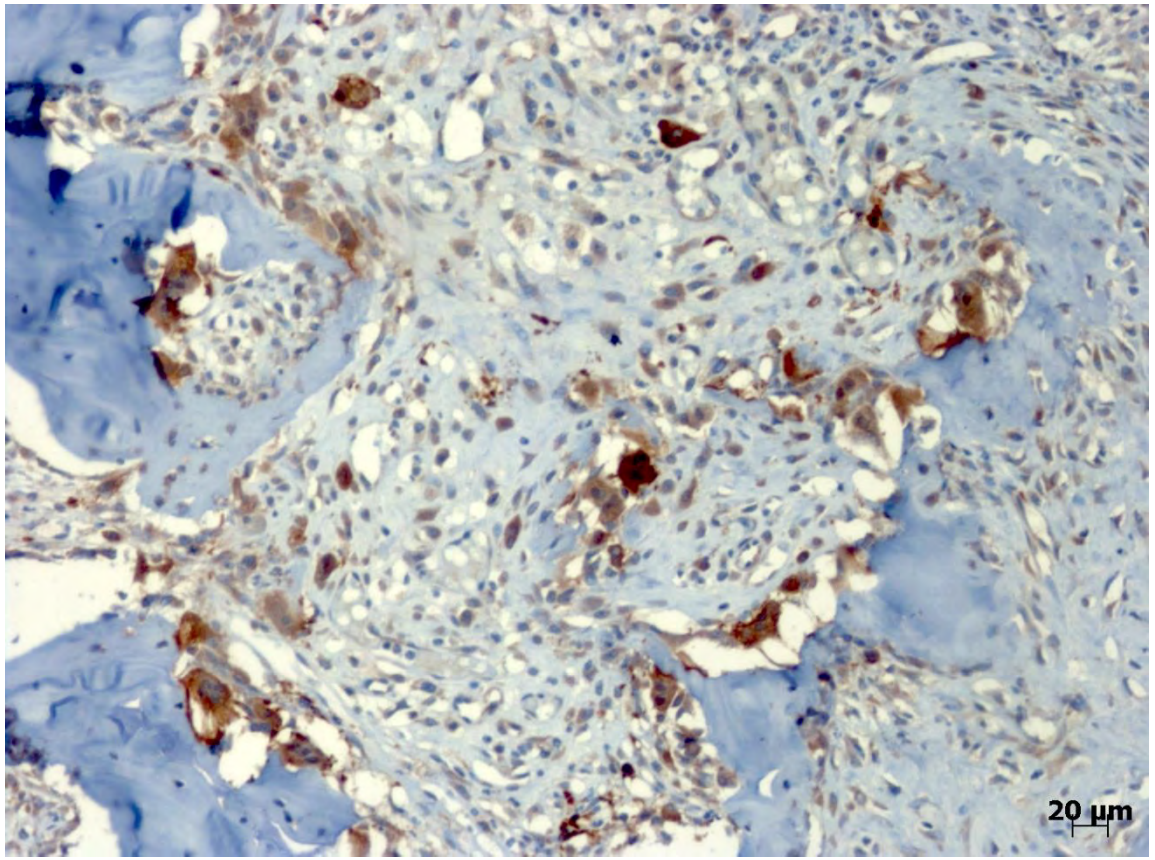
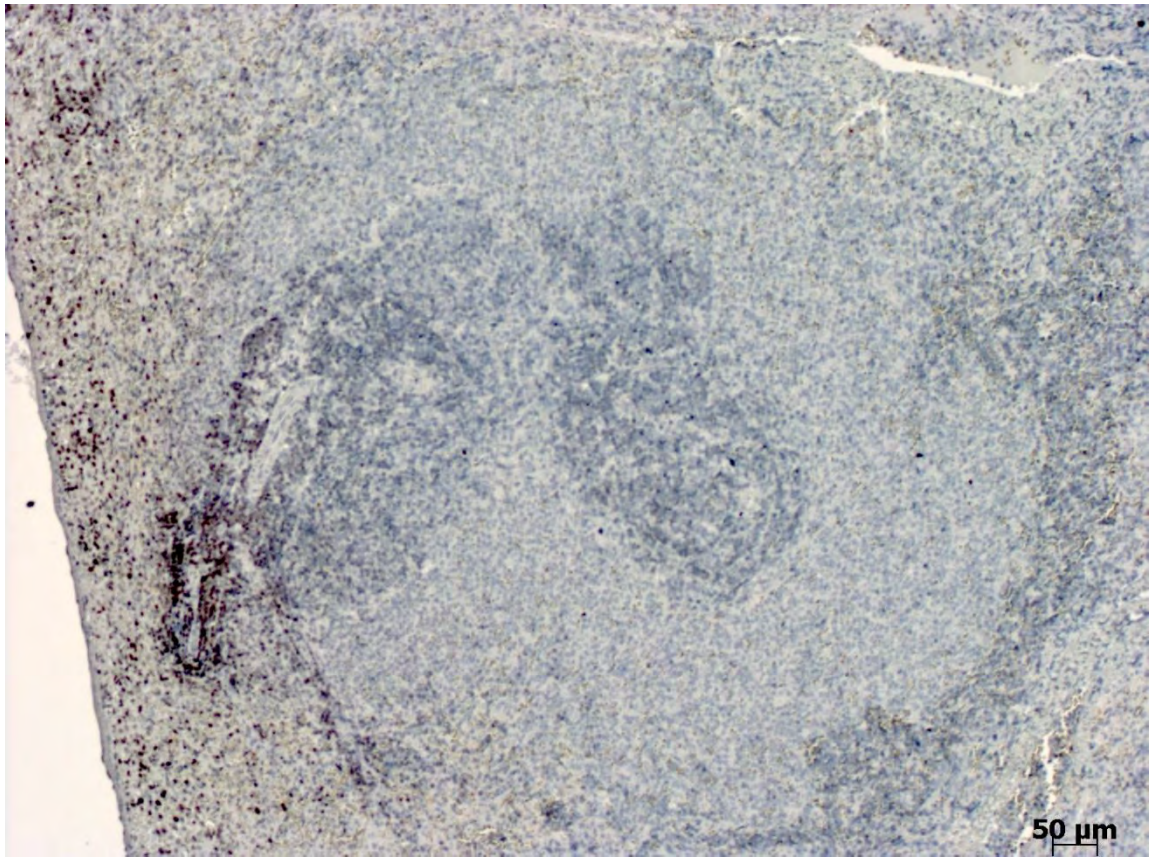
Structure/function alterations of one organ can result in structure/function alterations of other organ(s) and/or whole organism



Collagen induced arthritis, bone, MMP3 IHC



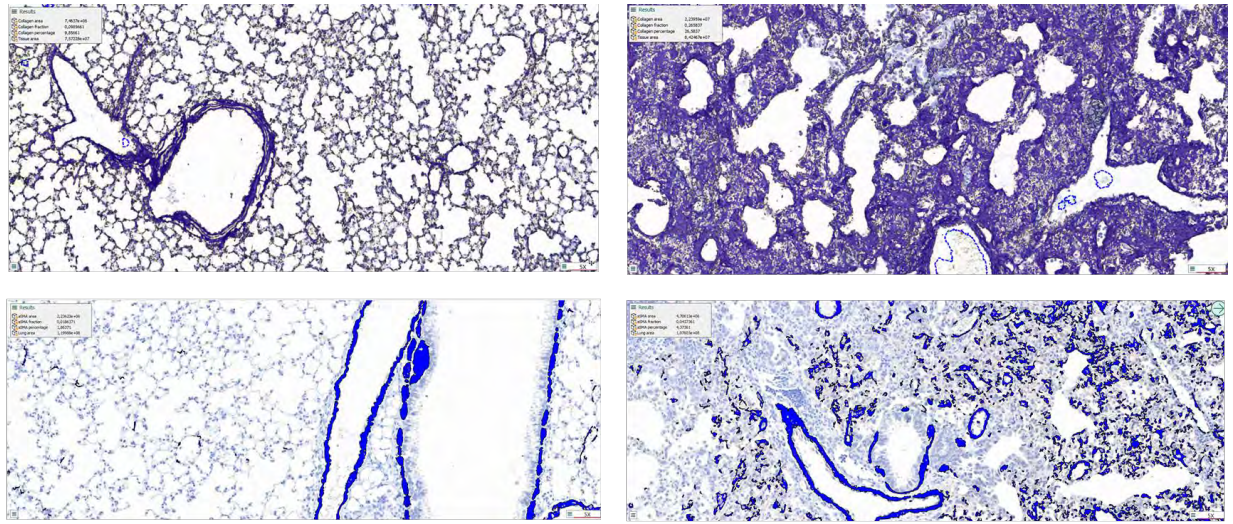
Collagen induced arthritis, spleen, target IHC

Animal model: Pathophysiology

Analysis: Quantitave Digital image analysis (DIA)

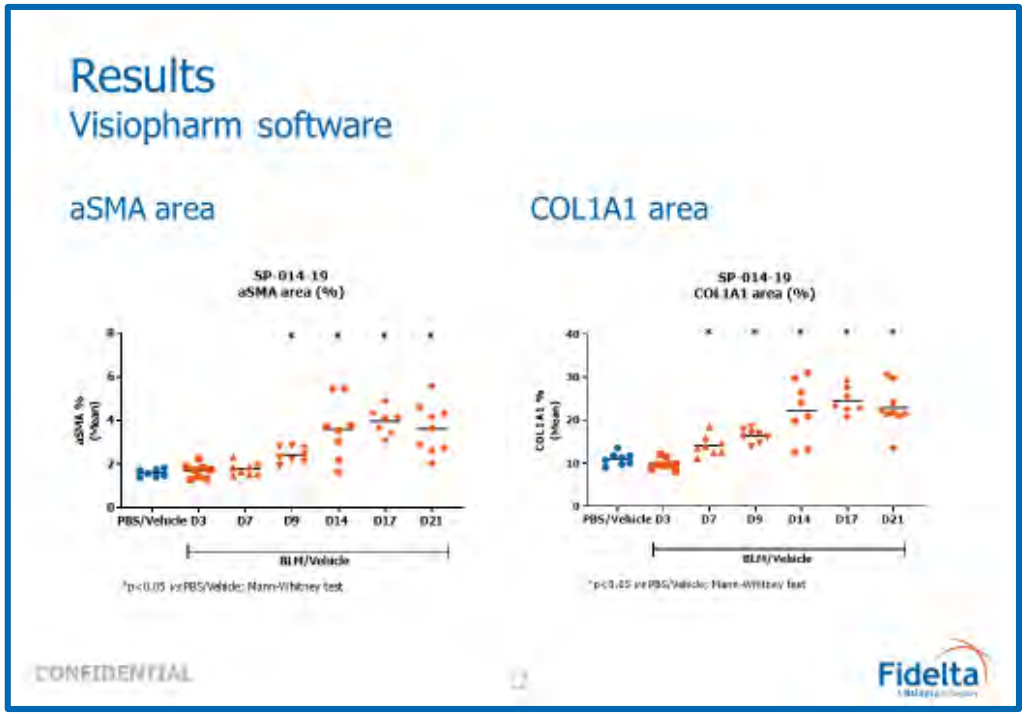
COL1A1, IHC

αSMA, IHC

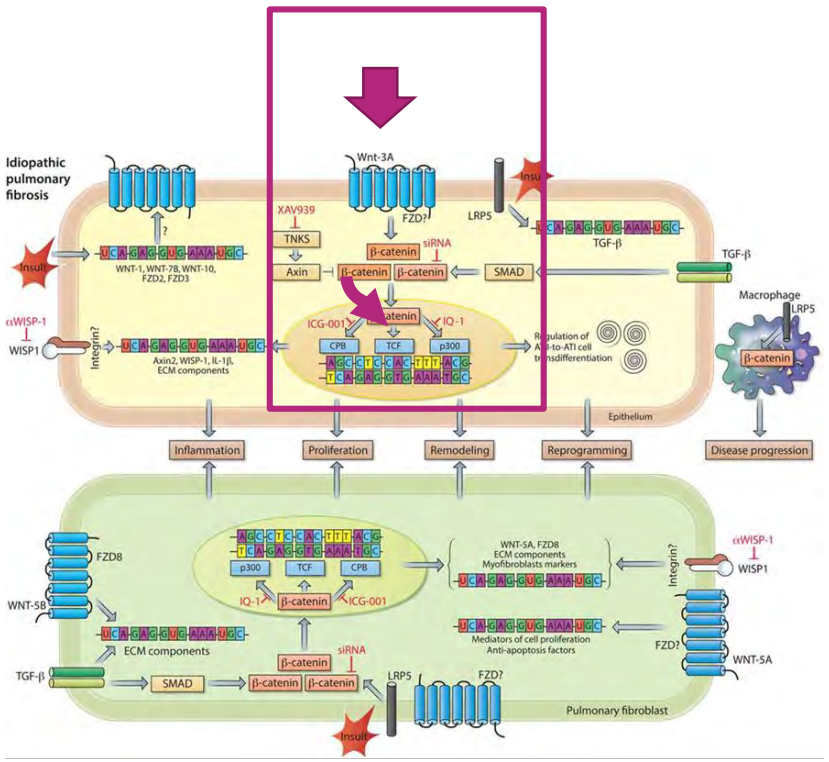


Negative control

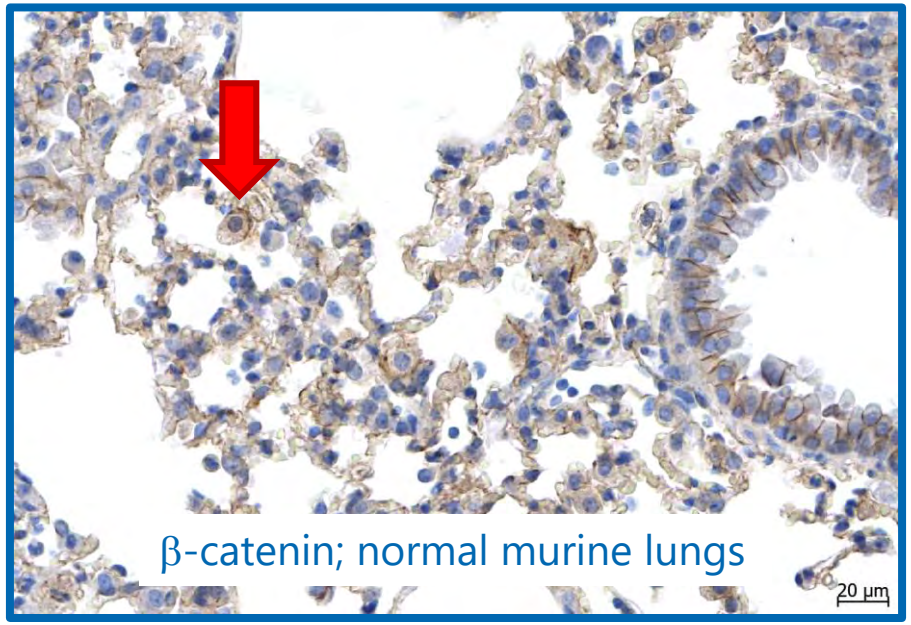
BLM+ vehicle group

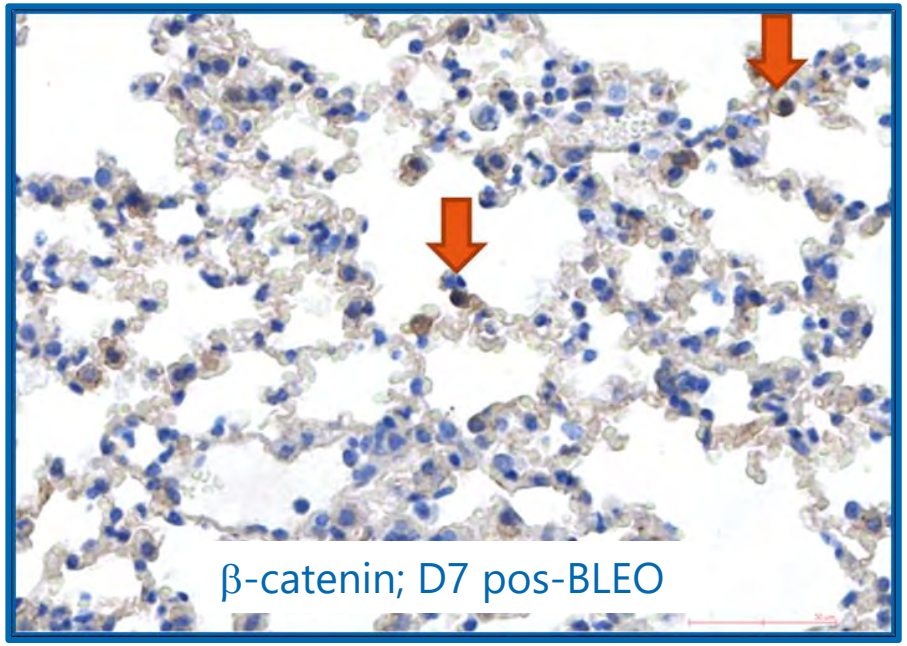


Animal model: Pathway validation

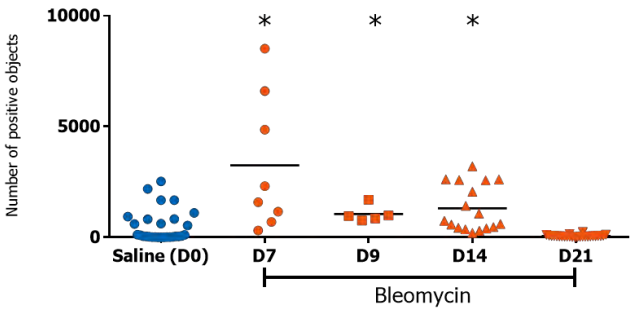


Thorax, 2017;0:1–14. doi:10.1136/thoraxjnl-2016-209753





Number of nuclear ß catenin positive cells per lungs through days



*p<0,05 vs D0; Mann-Whitney test

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Digital Localization and Quantification of WNT-3A Signalling-edited Target Approach in a 21 Day Murine Model of Idiopathic Pulmonary Fibrosis

Željka Anzulović, Snježana Čužić, Anja Ognjenović, Maja Antolić, Anamarija Markota, Boška Hrvačić, Ines Glojnarić

HDIR-5 Translating Science to Medicine: Targets and Therapeutics
November 8-10. 2018, Zagreb, Croatia

CONFIDENTIAL

Animal models: Efficacy

Selvita

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A translational value of pulmonary function tests in a mouse model of bleomycin-induced pulmonary fibrosis: effects of approved therapies Nintedanib and Pirfenidone

Željka Anzulović Šanta, Maja Antolić, Anja Ognjenović, Snježana Čužić, Ines Glojnarić, Boška Hrvačić
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Introduction

Pulmonary function tests (PFT's) routinely implemented in clinics are the first step in the diagnosis of idiopathic pulmonary fibrosis. Evaluation of PFT's in the mouse model of pulmonary fibrosis accompanied by histological readouts may improve clinical predictability of new therapeutic candidates. Forced expiration (FE) parameters are considered as the most predictive for restrictive pulmonary disorders.
The aim of the study was to estimate the translational value of the PFT technique in the established mouse model by evaluating the effects of two approved therapies for idiopathic pulmonary fibrosis, Pirfenidone and Nintedanib.

Materials & Methods

Bleomycin induced pulmonary fibrosis: Pulmonary fibrosis was induced in C57BL/6 male mice by intranasal application of 30 µg bleomycin. Both therapies were administered in preventive settings, from D0 till the end of experiment on D14. Nintedanib was administered at a dose of 60 mg/kg once daily, and Pirfenidone at a dose of 50 mg/kg twice daily. Fourteen days after bleomycin administration, pulmonary function measurements were performed and lungs were sampled for further pathohistological analyses.

Pulmonary function measurements: PFT's were assessed by using *in vivo* invasive lung function measurements system Buxco®- Forced Pulmonary Maneuvers®. Forced expiration tests (FE) were analyzed as main predictors of restrictive respiratory changes. Parameters as forced vital capacity (FVC), forced expiratory volume at 100 ms (FEV100) and peak expiratory flow (PEF) in combination with Pressure-volume and Flow-volume curves were the base of the interpretation.

Pathohistology: Paraffin embedded formalin fixed lung tissue were cut and stained according to Crossman. Matsuse modification of Ashcroft score (Eur Respir J (1999) 13:71-77) was used to evaluate fibrosis in lung specimens. Histology slides were scanned using Zeiss Axioscan.Z1 scanner. Myofibroblast (αSMA, IHC) accumulation and *de novo* collagen (COL1A1, IHC) deposition in lungs was assessed by digital image analysis (Calopix software, TRIBVN, France).

Statistical analysis: For all PFT's values, significance was analyzed in Buxco FinePointe software, by applying unpaired t-test. To define statistically significant differences of Ashcroft scores between bleomycin/vehicle and PBS/vehicle group, the evaluation was performed by Wilcoxon Signed Rank Test. Comparisons for immunohistochemical analyses were performed using Mann-Whitney Test (GraphPad Prism version 8.2.1). The level of significance was set at $p<0.05$ in all cases.

Conclusions

In contrast to Pirfenidone, Nintedanib treatment significantly improved PFT's parameters and Ashcroft score at day 14 post bleomycin challenge.

Significant correlation of functional tests and Ashcroft scores was confirmed.

Implementation of PFT, supported by the pathohistological evaluation could be a good platform to increase the translational value of the model.

Results

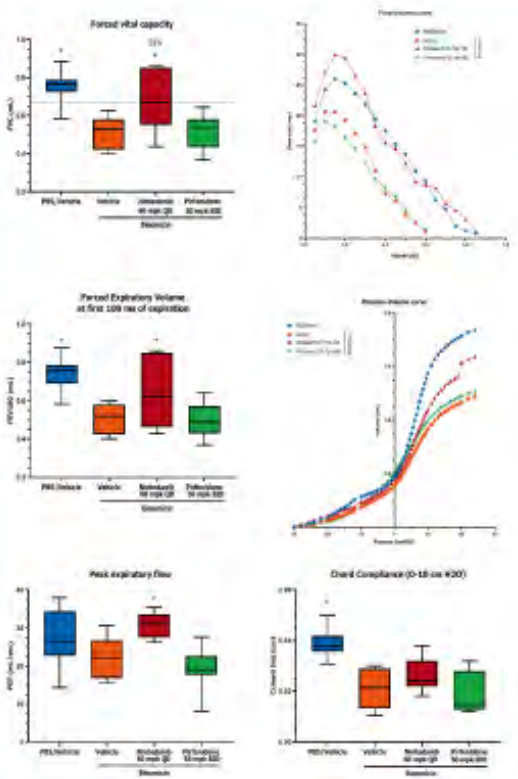

Figure 1. FE test curve with relevant parameters and P-V curve measured at D14 post BLM challenge. Significant improvement in group treated with Nintedanib in therapeutic regiment, observed at FVC (29% improvement over BLM/Vehicle), FEV 100, PEF supported by P-V and F-V curve trend.

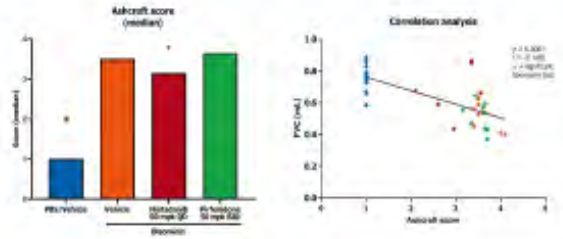

Figure 2. Ashcroft score; Nintedanib administration significantly attenuated Ashcroft score increased by BLM challenge. Significant Spearman's rank correlation dependence between histological Ashcroft score and PFT's FVC parameter values.

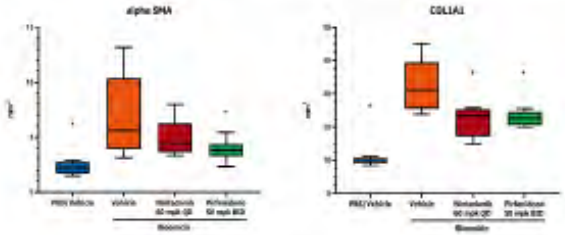

Figure 3. Digital pathology quantification results of α-SMA and COL1A1 positive lung surface; Pirfenidone therapy significantly reduced myofibroblast accumulation and collagen synthesis, while Nintedanib effect was more prominent on attenuation of collagen deposition.

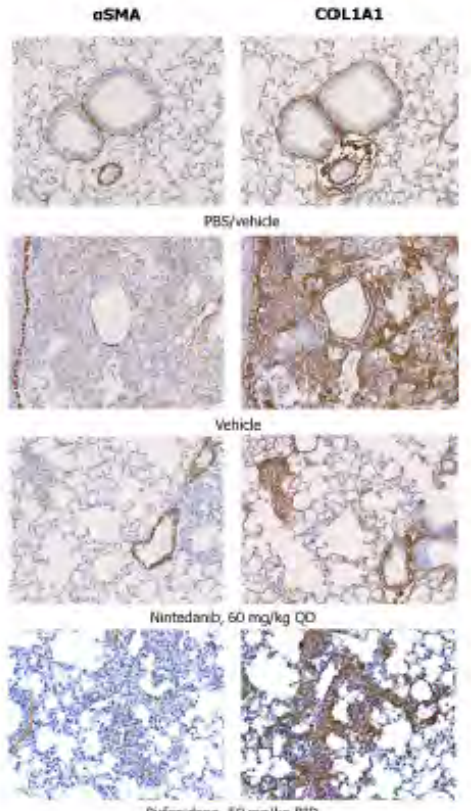

Figure 4. Representative pictures of myofibroblast (αSMA, IHC) accumulation and *de novo* collagen (COL1A1, IHC) deposition into alveolar wall and intra-alveolar space on D14 post bleomycin administration (Calopix software, TRIBVN, France). In Pirfenidone treated animals, elevated collagen accumulation and presence of inflammation cells is observed in alveolar space, while Nintedanib shows effect on resolution.

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ERS, Madrid 2019

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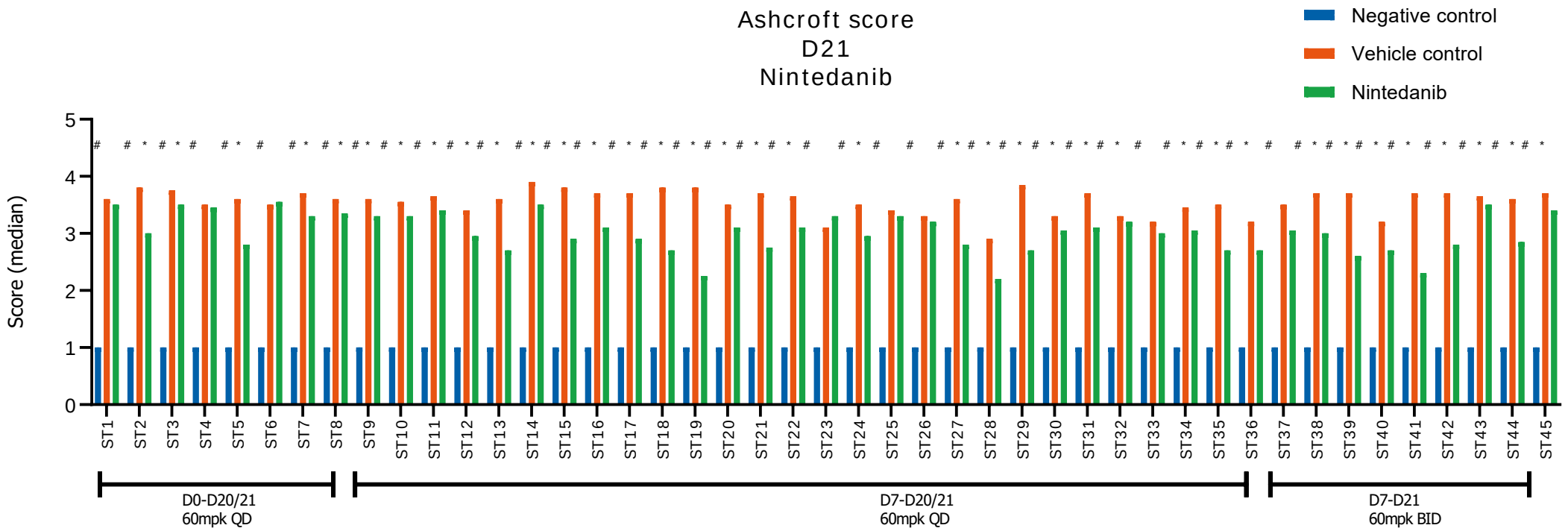
Bleomycin induced lung fibrosis: Ashcroft score



#p<0.05 *vs* Vehicle control; Wilcoxon Signed-Rank Test
*p<0.05 *vs* Vehicle control; Mann-Whitney Test

Animal model: Data integration

RSV A2-19F infection model in BALB/c female mice

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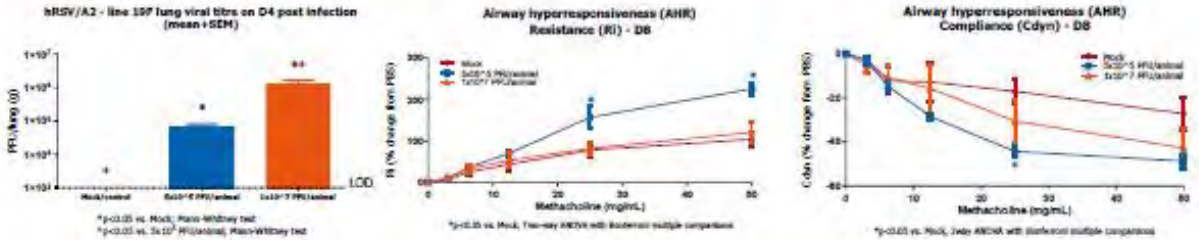
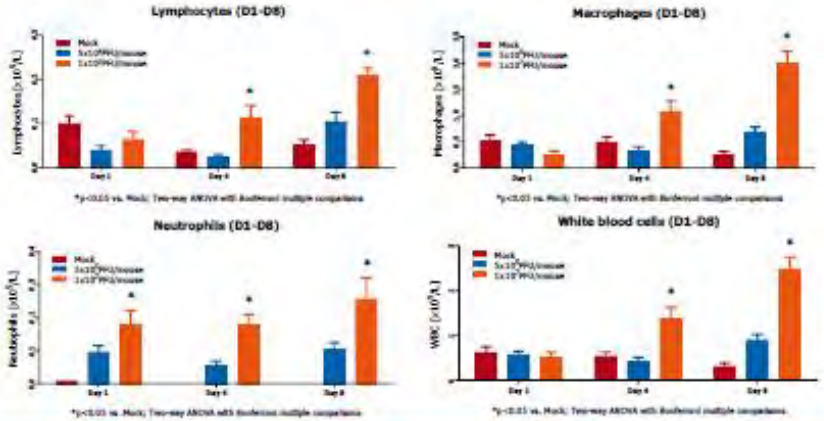
- Enhanced body weight change and clinical scores
- Enhanced inflammation and mucus production
- Enhanced bronchial and alveolar damage
- Enhanced airway hyperresponsiveness (AHR)
- Enhanced viral load

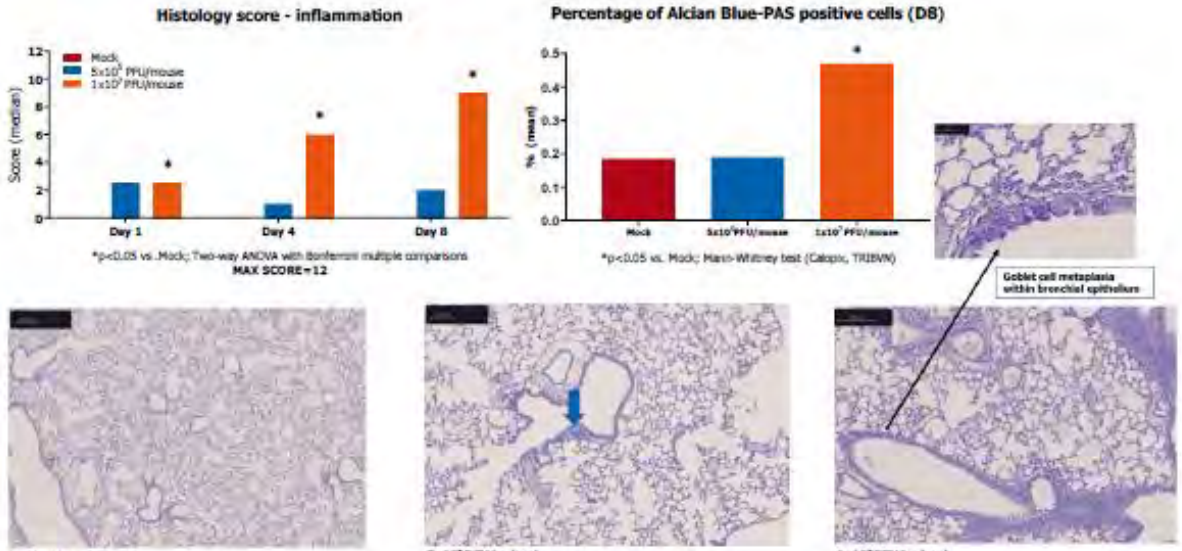
Lung viral load and airway hyperresponsiveness



Bronchoalveolar lavage fluid (BALF) cell count

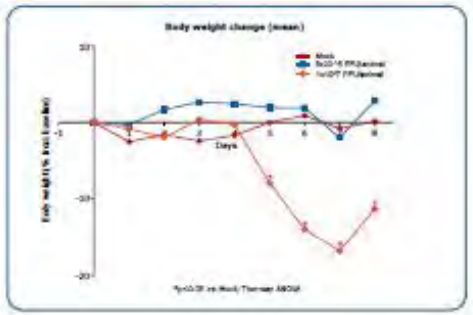


Histopathology



Read-outs:

- Airway hiperresponsiveness (AHR)
- BALF cell count
- BALF cytokines
- Body weight change
- Clinical scores
- Histopathology
- Lung viral load



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Animal model: Integrated data interpretation

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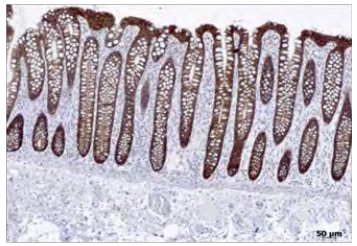
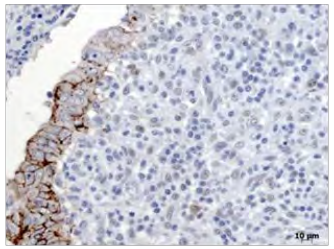
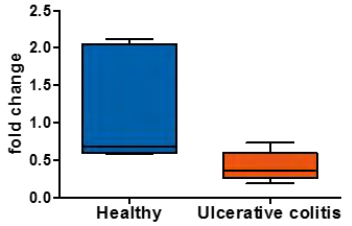
Claudin 3 – Healthy vs. IBD

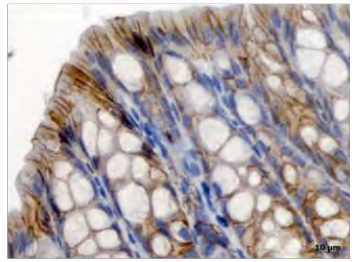
Human

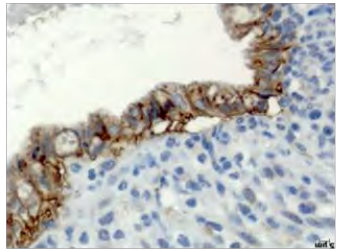


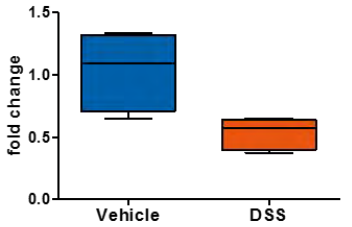




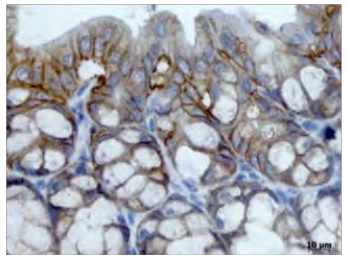
DSS

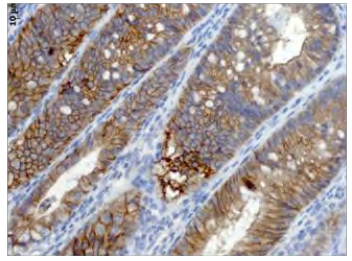


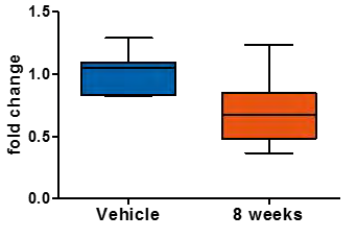




Adoptive







EUSTIM, Wien 2014

Animal models: Mode of action

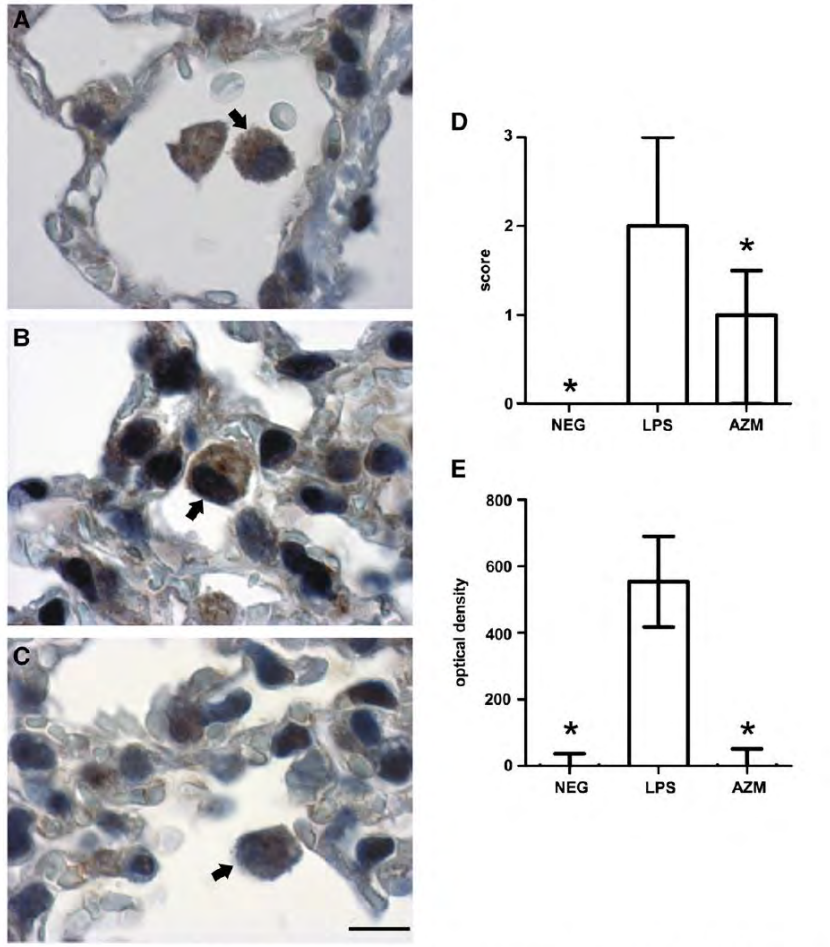


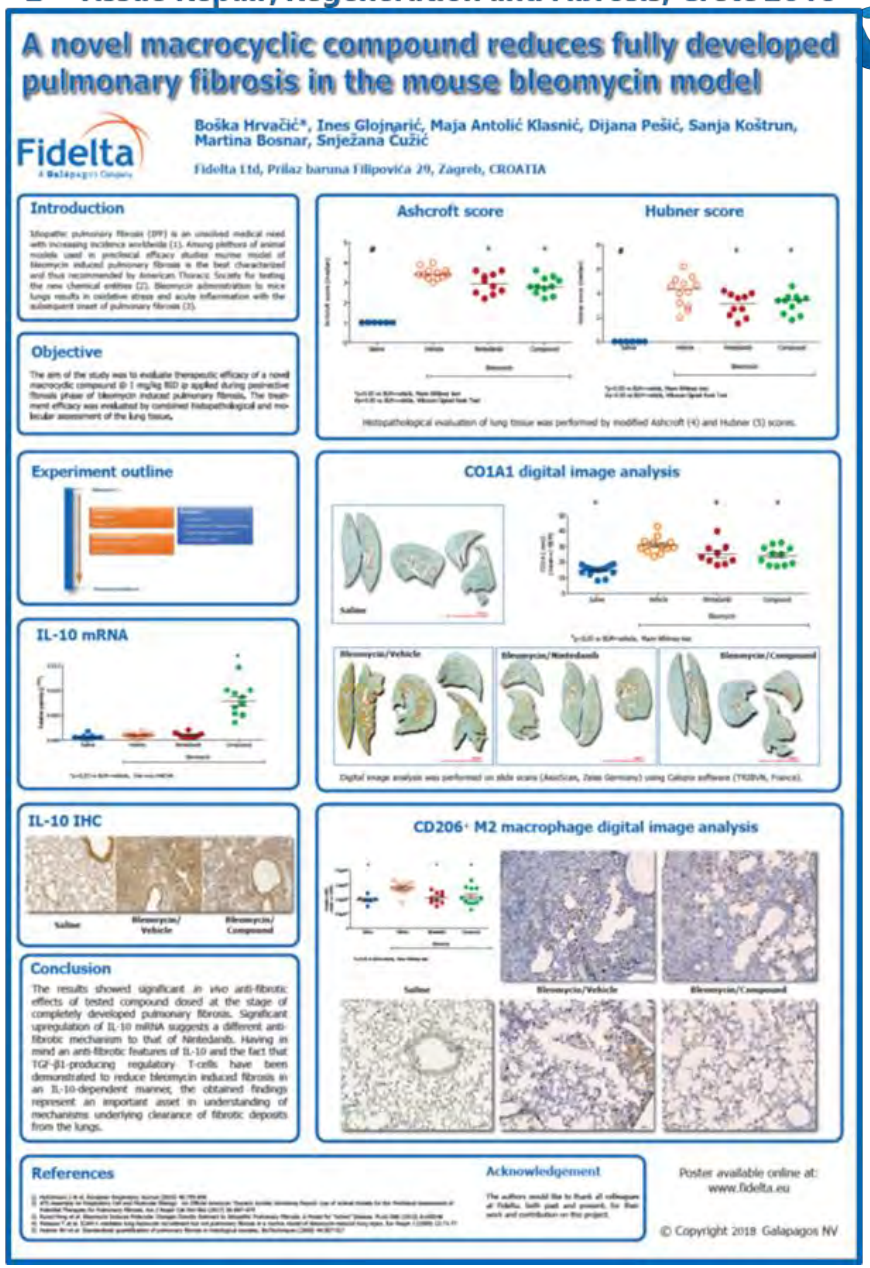
Fig. 3. Azithromycin treatment inhibited LPS-induced AP-1 activation in alveolar macrophages. Immunohistochemical detection of AP-1, 4 h after challenge with PBS (NEG) (A) or 2 μg of LPS (B and C). In tissue sections from LPS-challenged vehicle-treated animals (LPS), positively stained alveolar macrophages were observed (B). Azithromycin treatment (200 mg/kg, i.p.) (AZM) reduced AP-1 nuclear staining (C). Magnification 1000×. Scale bar, 10 μm. Quantification of nuclear AP-1 staining was done by scoring (D) and determination of optical densities of all macrophages present on three random fields (E). Scores are presented as median ± range. Optical densities are presented as means ± S.E.M. The asterisk (*) indicates significant difference ($P<0.05$) from LPS-challenged vehicle-treated animals, Mann Whitney test.

Please cite this article as: Bosnar M, et al, Azithromycin inhibits macrophage interleukin-1β production through inhibition of activator protein-1 in lipopolysaccharide-induced murine pulmonary neutrophilia, Int Immunopharmacol (2011), doi:10.1016/j.intimp.2010.12.010

Analysis: Semi-quantitave; Score

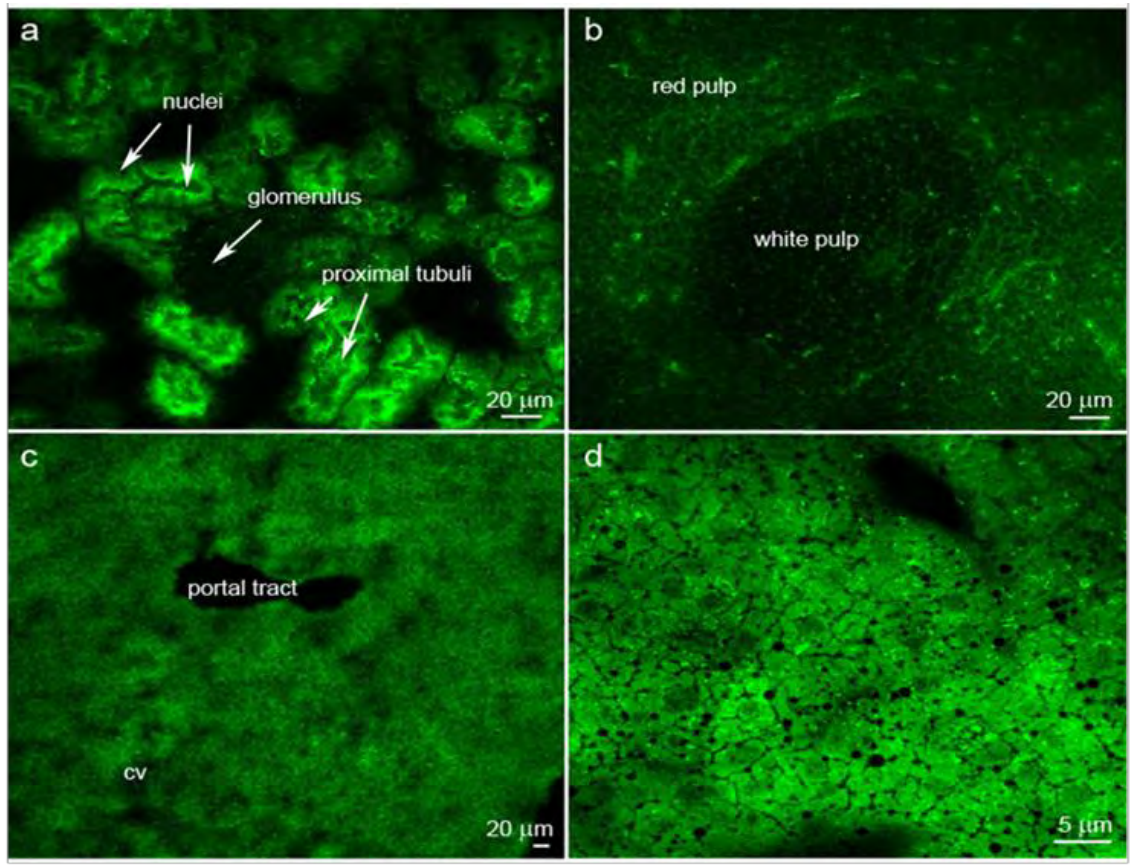
2nd Tissue Repair, Regeneration and Fibrosis, Crete 2018

Selvita



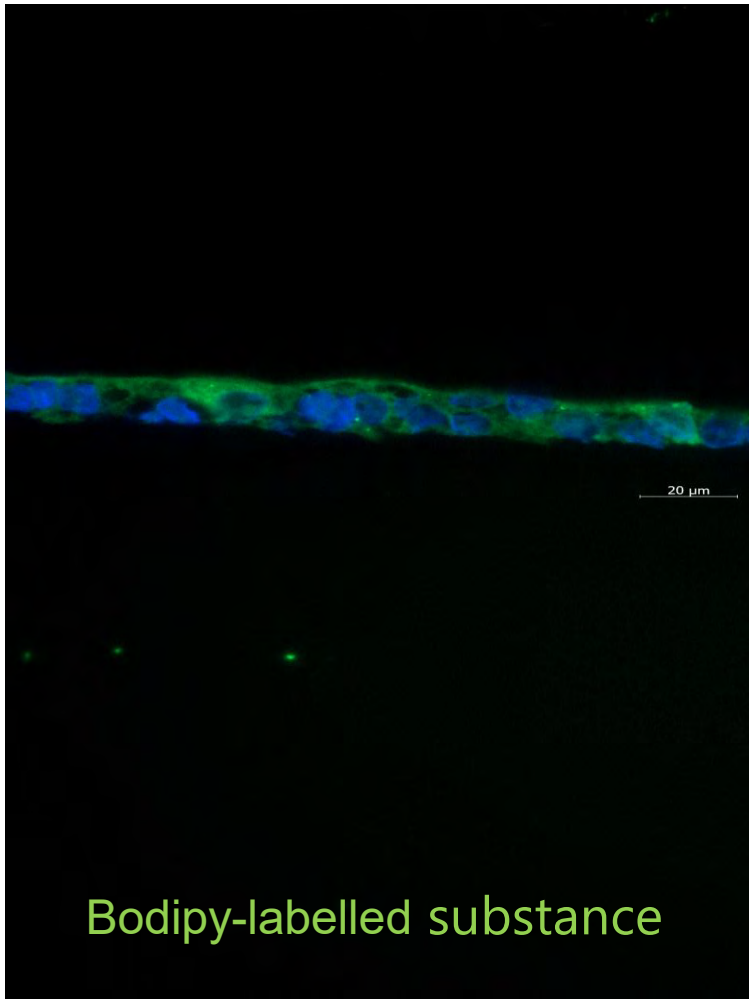
Analysis: Quantitave; DIA

Drug distribution: Organ/tissue/cell type



Azithromycin in kidney, spleen and liver 2 hours after *iv* application

Matijašić *et al.* Pharmacol Res (2012) 66:332-342



Oligonucleotide distribution: Organ/tissue/cell type

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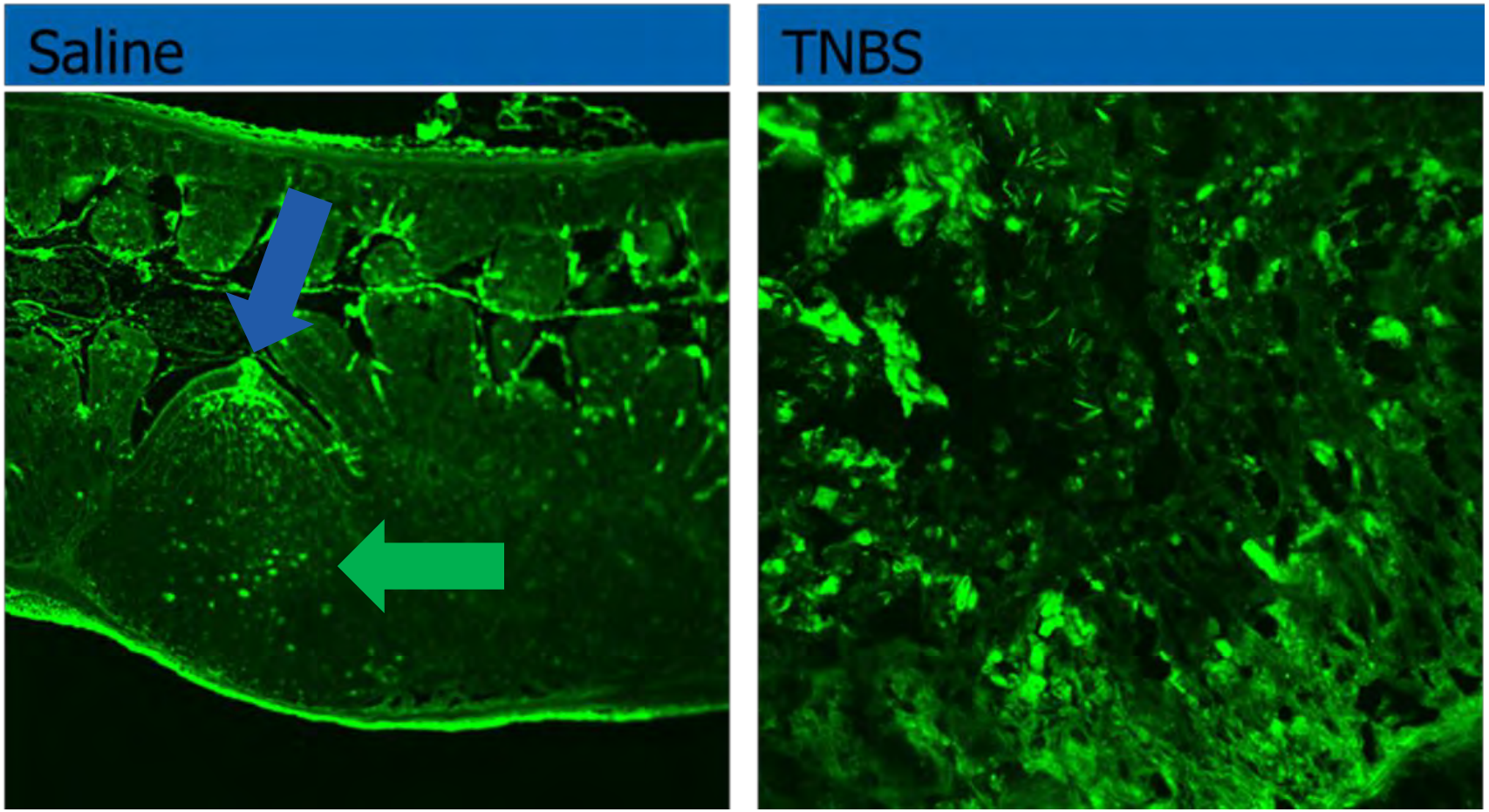
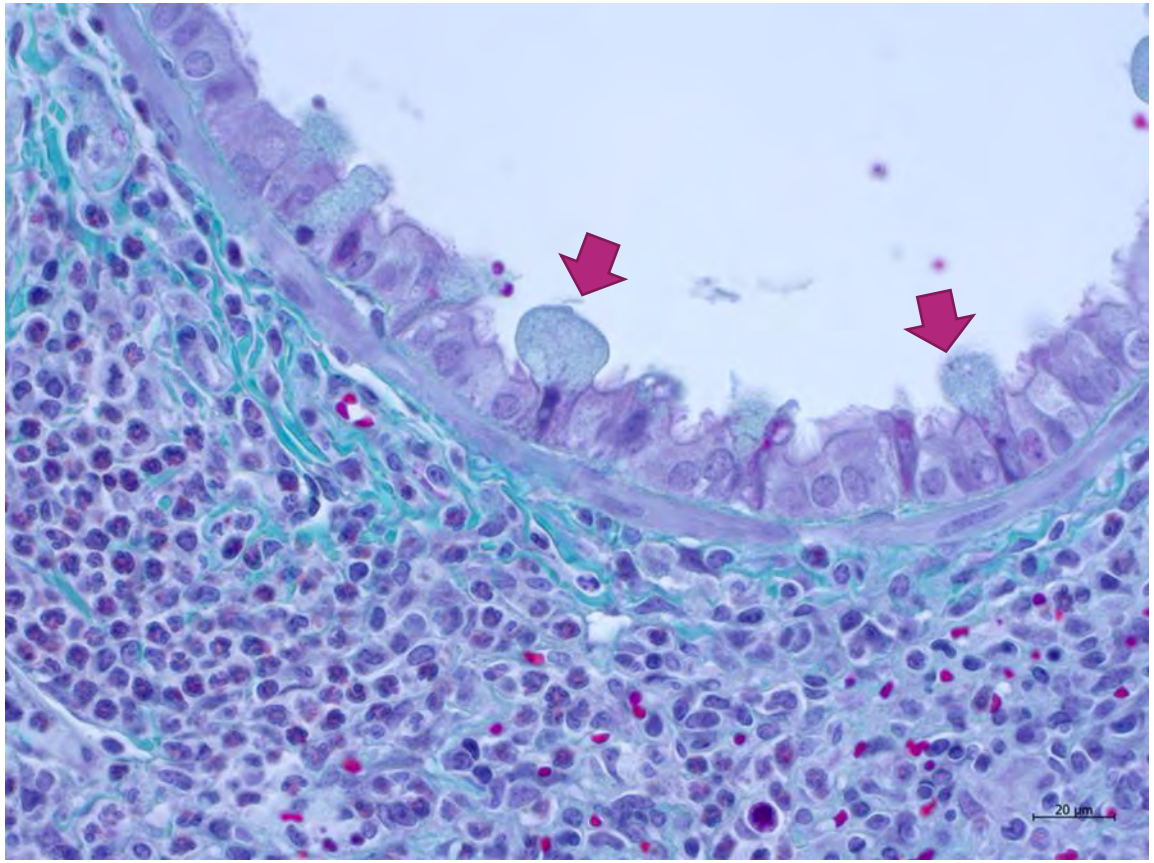


Intestinal lymphoid tissue M-cells

Animal models: Adverse effects
Vehicle & tested compounds



Fidelta

Evaluation of Hydroxypropyl-beta-Cyclodextrin (HPβCD) as formulation vehicle for use in general toxicity studies in mice

Ines Glojnarić, Snježana Čužić and Darko Marković
Fidelta Ltd., Zagreb, Croatia

Introduction

The standardization of vehicle use across the industry is hindered by the varied physicochemical properties of new chemical entities in development and tendency of a sponsor to use vehicles with which they have previous experience (1). Moreover, a survey of the pharmaceutical industry revealed highly divergent vehicle use (2).
Since unexpected vehicle-related toxicities can be difficult to segregate from NCE-related toxicities, there is a need for critical assessment of the vehicle suitability prior to use in safety studies.
HPβCD is a commonly used pharmaceutical excipient, well tolerated in humans and considered non-toxic following oral administration (3, 4). However, limited data is available to support use of HPβCD in toxicology studies in mice.

Objective

The aim of the present study was to evaluate the usefulness of HPβCD as a vehicle in repeat-dose preclinical safety studies in mice.

Materials and Methods

1000 mg/kg of HPβCD (Roquette, Italia S.p.A.) in purified water (10% w/v, pH3) has been administered by the oral route (gavage) to male CD1 mice for 5 days, UID or BID. Animals were sacrificed at D6.

Clinical Observations

On D1, between 30 and 90 minutes after administration, and on D5 the animals were submitted to a full clinical examination outside the housing cage, including functional and neurobehavioral tests.
Animals were weighed on D1 and D5.

Clinical Biochemistry

Activity of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP), as well as concentrations of total bilirubin and total cholesterol were determined in serum using Olympus AU400 Clinical Chemistry Analyser.

Histopathology

Livers were weighed, fixed in formaldehyde, paraffin embedded and stained with hematoxiline-eosine.

Results

Clinical Observations

Mortality / Morbidity: No death occured during the study
Clinical signs: No clinical signs were observed during the study

Results

Clinical Biochemistry

Formulations containing HPβCD induced severe increase in serum aspartate- (AST) and alanine (ALT) aminotransferase activity compared to saline control. More pronounced effects were observed in animals dosed twice daily (40-fold increase in AST activity and 15-fold increase in the mean ALT activity).
There were no changes in the mean total bilirubin and cholesterol concentrations in serum of animals treated with HPβCD as compared to saline control.

Results

Histopathology

No significant increase in liver weight was observed.
In both groups treated with HPβCD moderate to severe necrosis was noted in hepatic acinar zone 2 and acinar zone 3. Atrophic hepatocytes in acinar zone 2 were recorded in animals treated with HPβCD once daily.

Discussion

In order to evaluate the use of HPβCD as a pharmaceutical excipient, numerou toxicological studies on laboratory animals have been performed. It has been noted, th in laboratory rodents oral HPβCD administration at a dose of ≥1000 mg/kg/day can induc elevation of liver enzymes in plasma. In male CD1 mice receiving 1000 mg/kg HPβCD f 13 weeks, ALT activity in serum was elevated, but this finding was not accompanied b alterations in liver morphology (1). In rats, HPβCD applied orally for 7 days at a dose o 4500 mg/kg/day 45% w/v and 14 days at a dose of 2250 mg/kg/day 45% w/v, induce elevation of liver enzyme levels in plasma (ALT, AST, GLDH) without any histopathologic changes (5).

Conclusion

It is suggested, based on the presented results, that formulations containing HPβC should be used with caution in mice since HPβCD may induce hepatocyte necrosi accompanied by severe elevation of serum transaminase activity. These findings could b of critical importance for interpretation of data in preclinical safety studies in mice.

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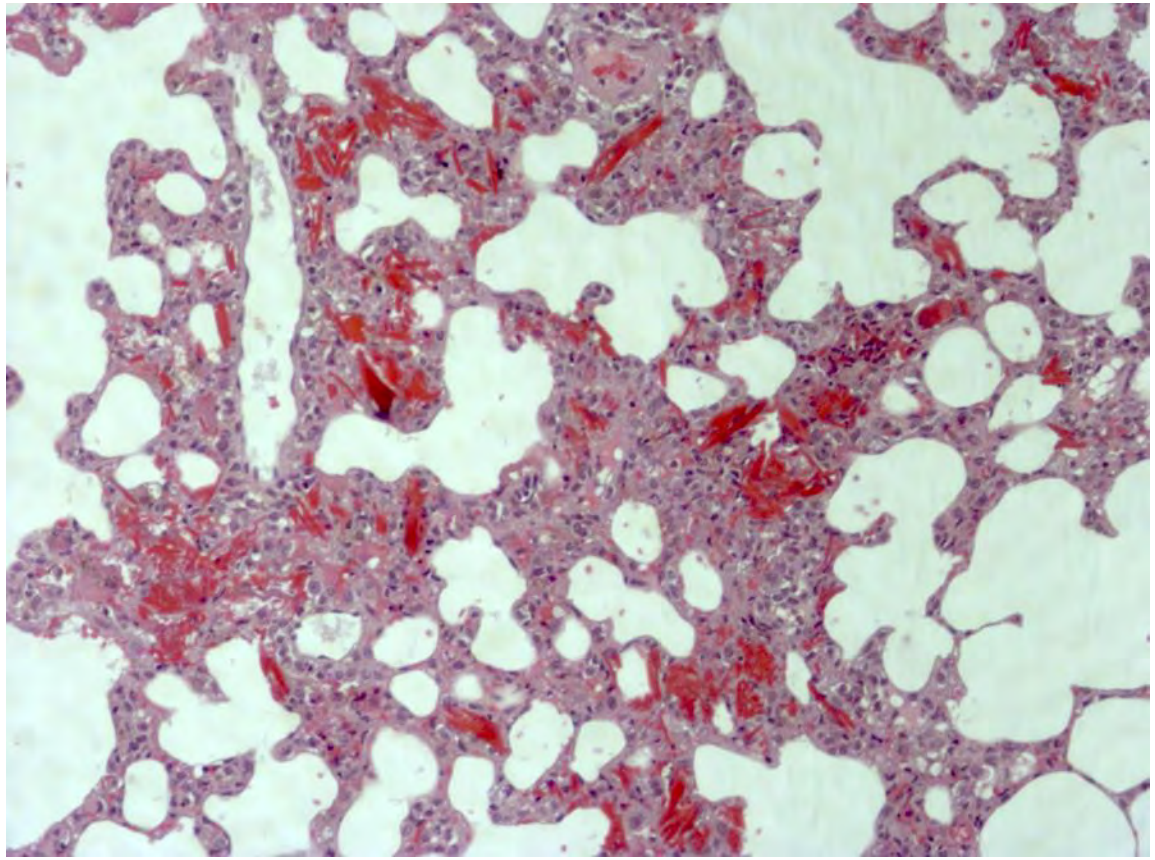
Abstracts / Toxicology Letters 221S (2013) S59–S256

Selvita

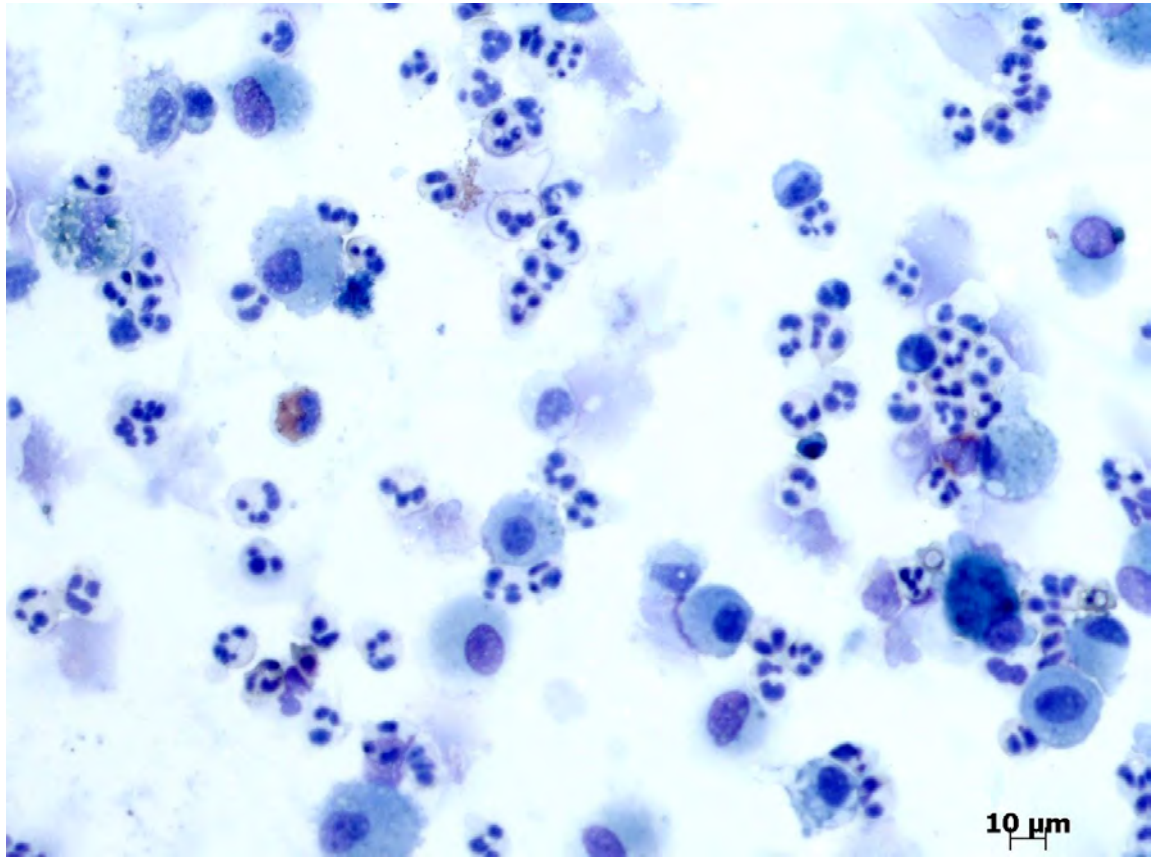
Toxicologic studies



Toxicologic pathology is a medical discipline that applies the professional practice of pathology—the study of diseases—to toxicology—the study of the effects of chemicals and other agents on humans, animals, and the environment. Toxicologic pathology professionals work in academic institutions, government, the pharmaceutical and chemical industry, contract research organizations or as consultants, and utilize traditional clinical or anatomic pathology endpoints, as well as contemporary advances in molecular and cellular biology. They are dedicated to the integration of toxicologic pathology into hazard identification, risk assessment, and risk communication regarding human, animal, and environmental exposure to potentially toxic substances.

https://www.toxpath.org/index.asp

Clinical studies



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Modulation of neutrophil and inflammation markers in chronic obstructive pulmonary disease by short-term azithromycin treatment

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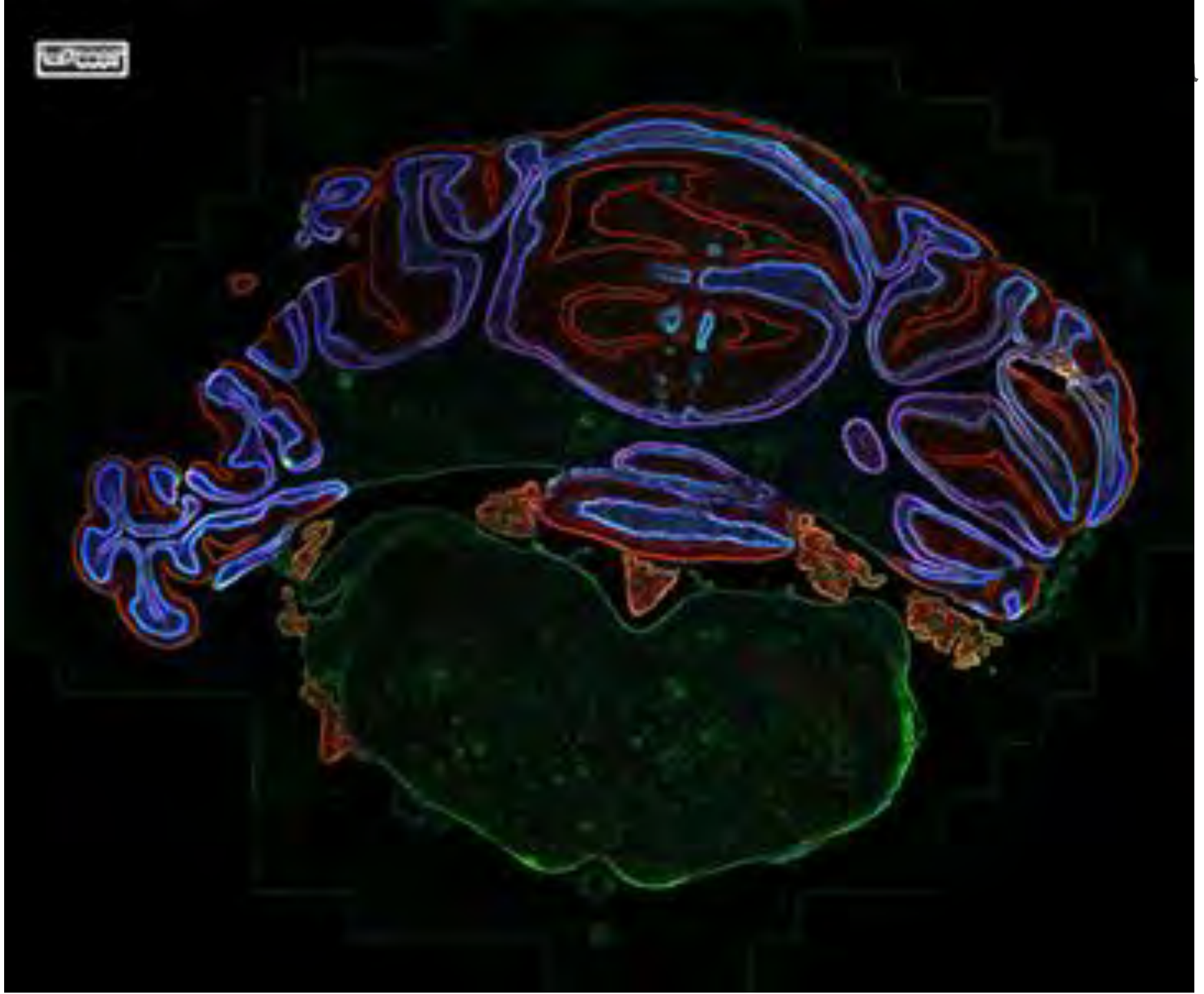
Sampling & Fixation

- Fasting prior sampling
  - **Liver**
- Formalin perfusion/inflation
  - **Brain**
  - **Lungs**
- Sampling
  - **Time frame**
  - **Be gentle!!**

- FormalFixx
  - **Two parts formalin + eight parts of water**
  - pH < 6
- Specimen dimensions
  - **3-4 mm thick**

- Fixative : tissue ratio
  - Lowest acceptable ratio 20:1
  - **Target ratio 50:1**
- Duration of fixation
  - **Guidelines 24-72h in formalin**

Tissue staining methods used for patho-histological evaluation



Tissue processing: Tissue sectioning

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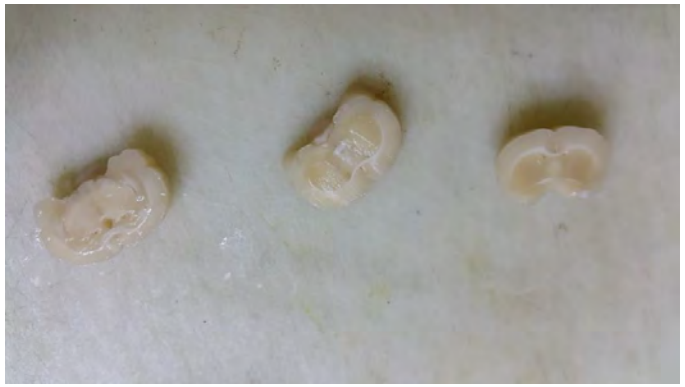
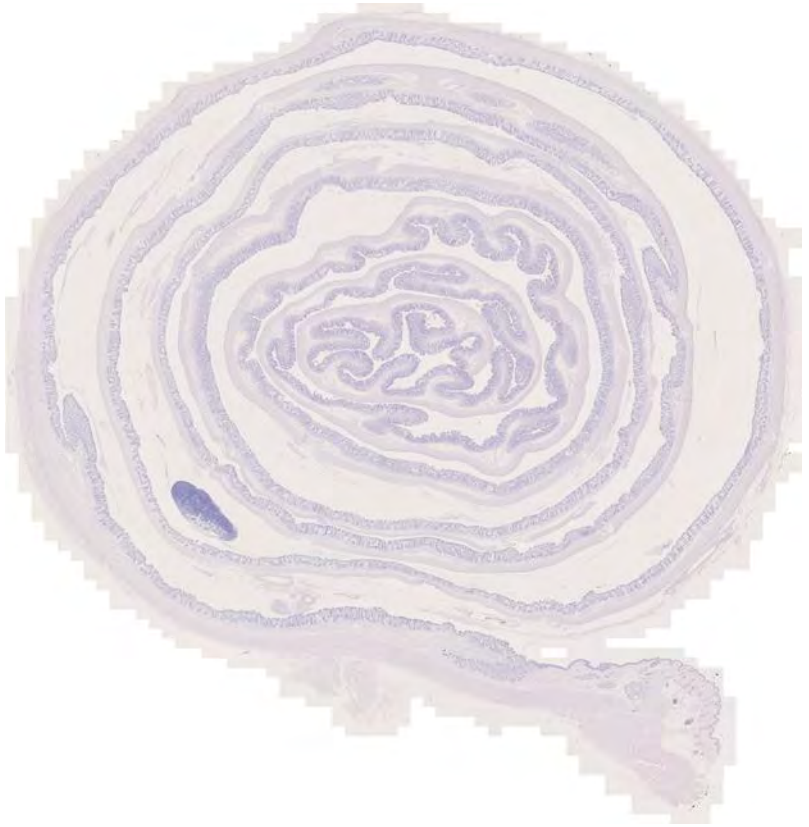
Brain, serial sections



Intestine, swiss-rolls



Staining methods

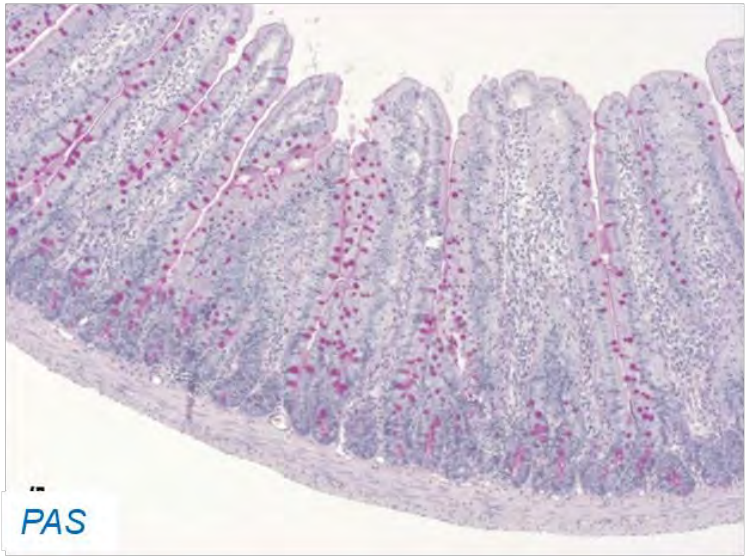
Histochemistry

Chemical reaction between chromogen and chemical entities in tissue

- salt formation

"Visualization" of

- Structural/functional molecules in tissue
  - Proteins, mucopolysaccharides, fat
- Cells/cell types by highlighting their "chemical" properties
  - Mastocytes, goblet cells, osteoclasts



Immunohistochemistry

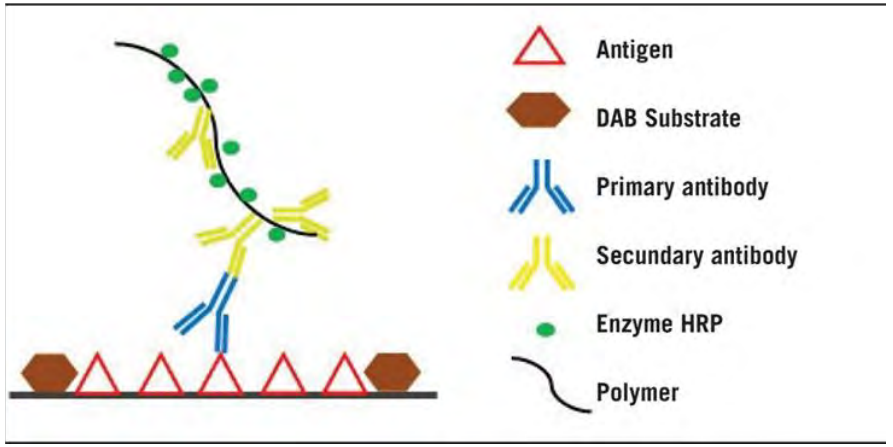
Reaction between specific antibody and antigen in tissue

"Visualization" of

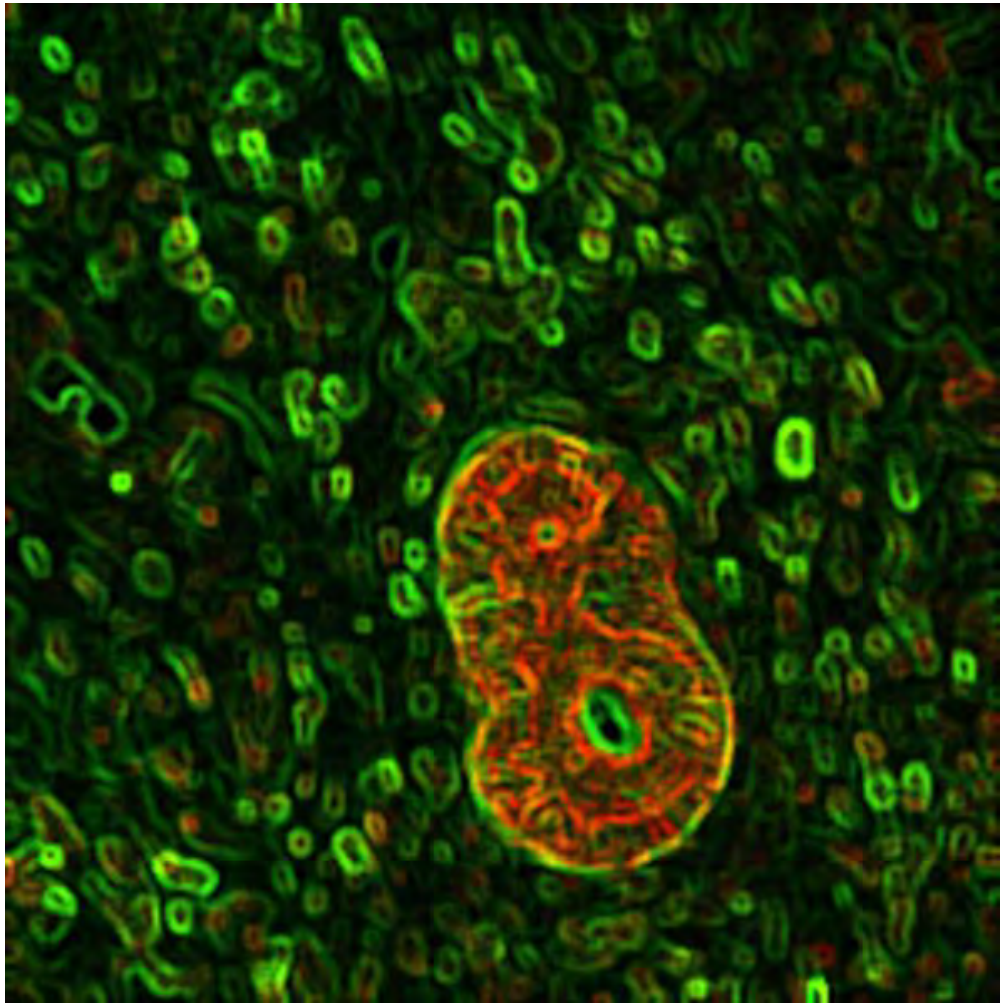
- Structural/functional proteins in tissue

Accentuation of

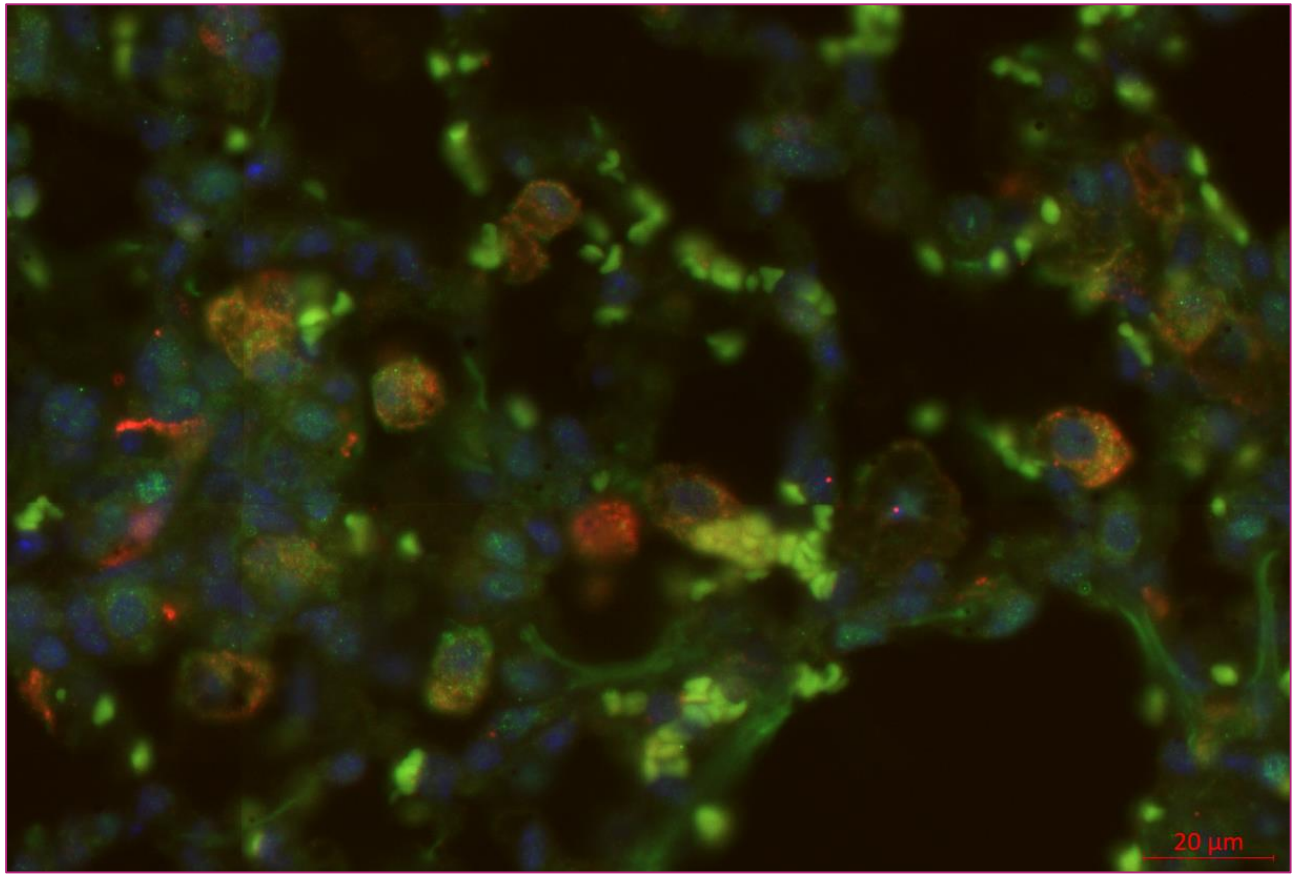
- Certain cell-types
- Functional status of cells



Staining methods: Immunofluorescence (IF) / Double IF

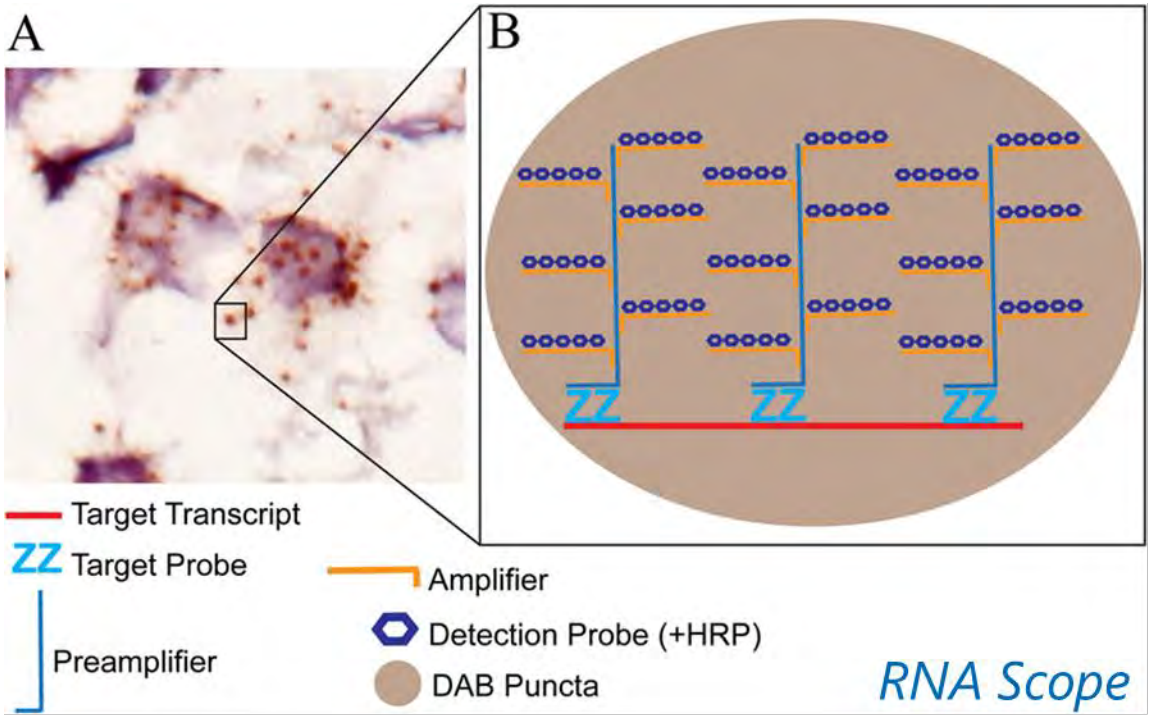


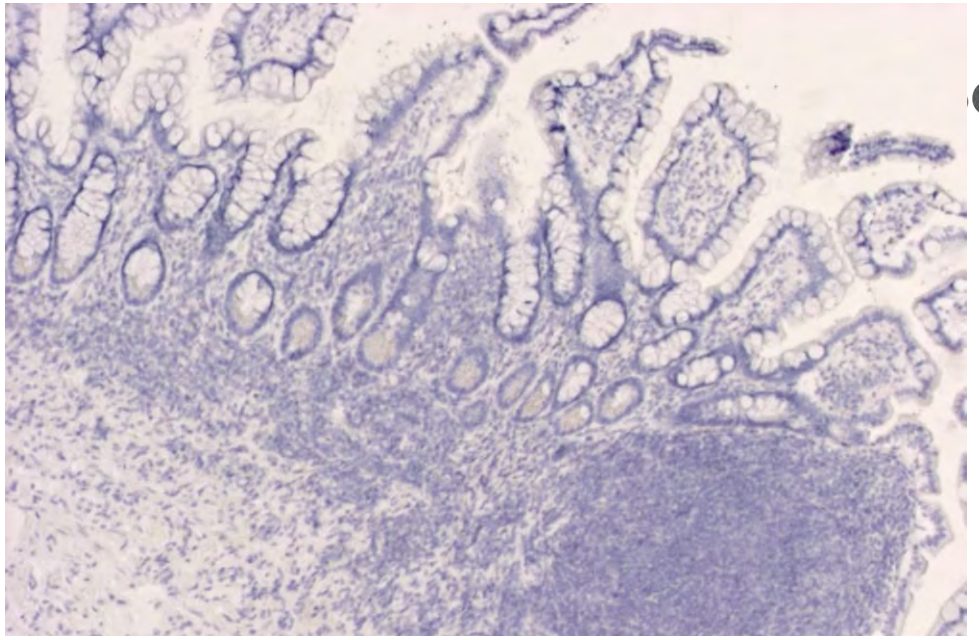
IBD, target/cell marker



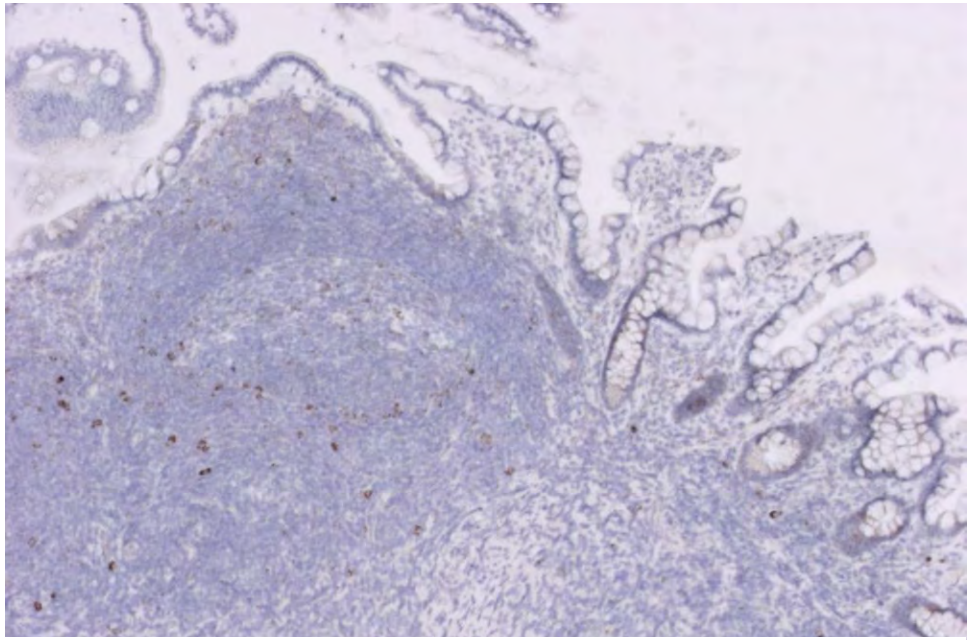
Bleomycin induced lung fibrosis; target/CD206

Staining methods: *In situ* ***hybridization***



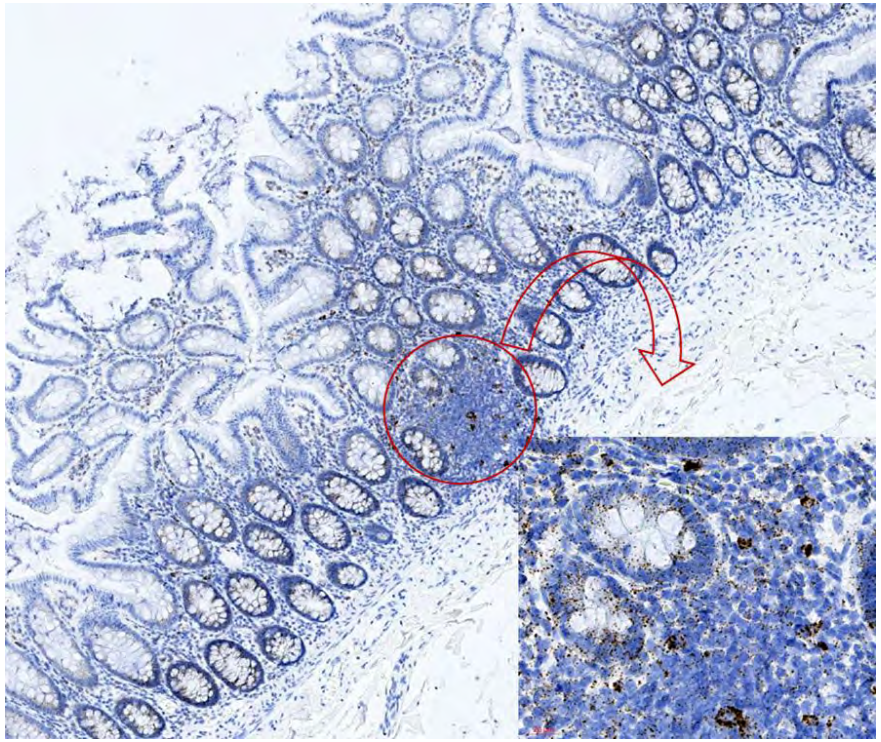


Negative control; non-mammalian RNA

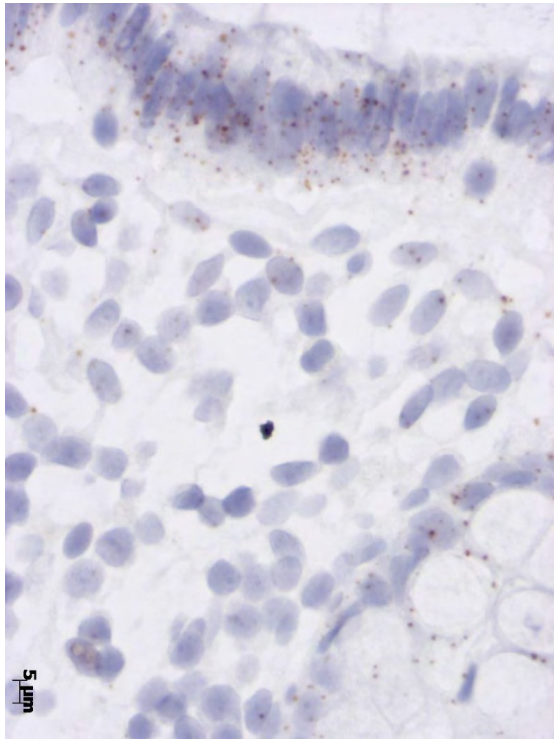


Positive control; PPIB-RNA

Staining methods: *In situ* ***hybridization***



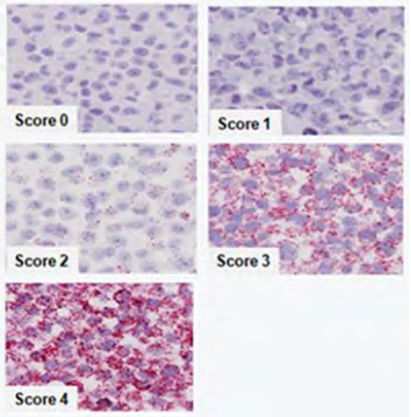
Positive control; PPIB-RNA



Target mRNA

Scoring system

Score	Criteria
0	No staining or <1 dot/10 cells
1	1-3 dots/cell
2	4-9 dots/cell. None or very few dot clusters
3	10-15 dots/cell and <10% dots are in clusters
4	>15 dots/cell and >10% dots are in clusters



Special pathology methods

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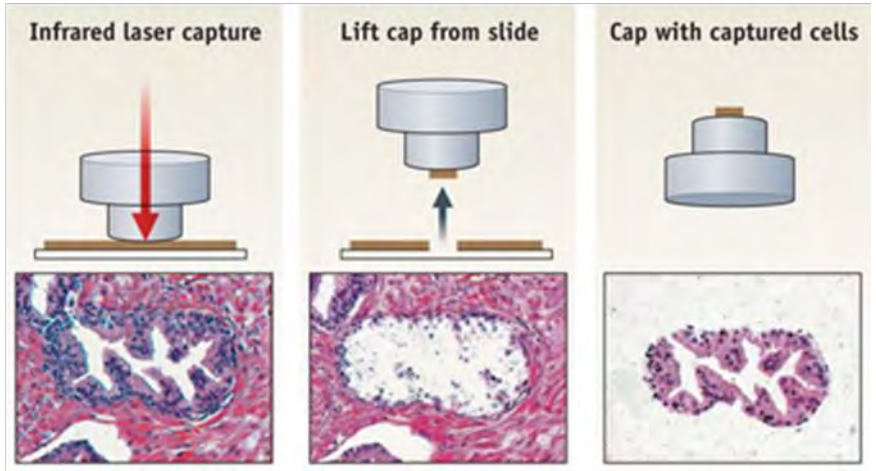
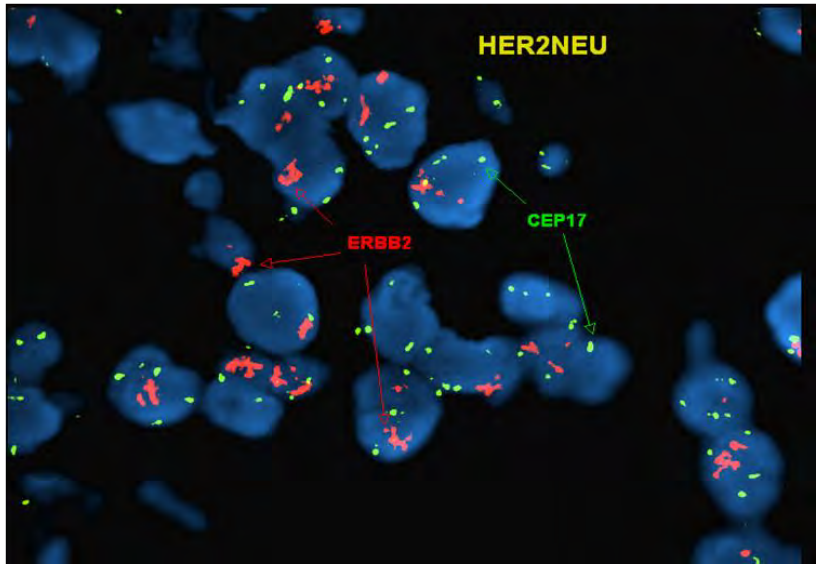
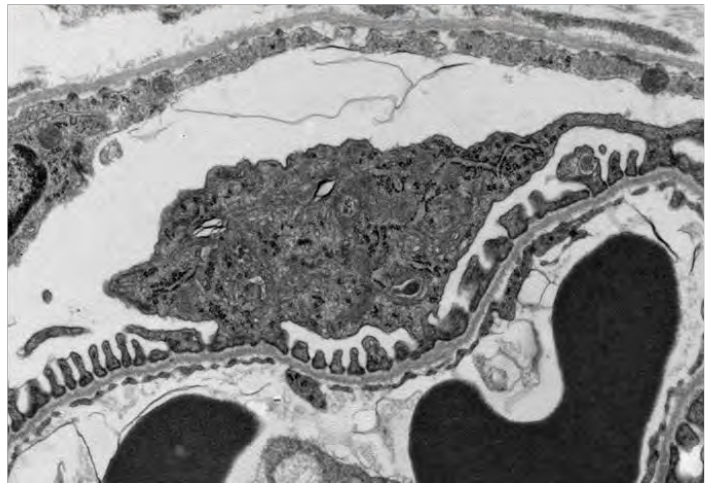
Laser microdissection



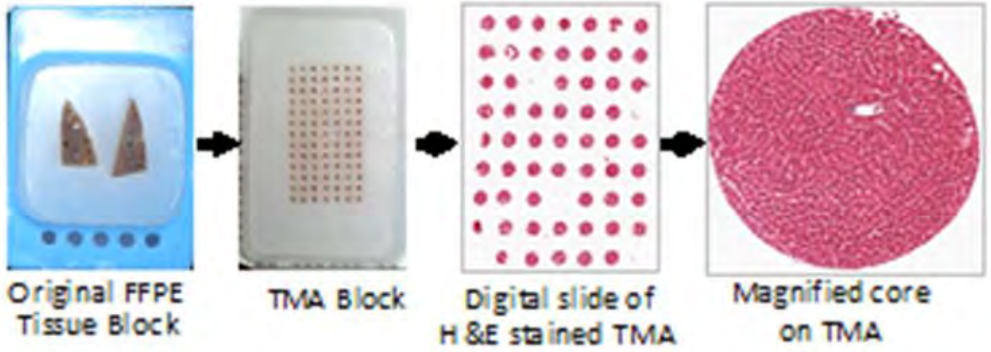
Flourescence *in situ* hybridization



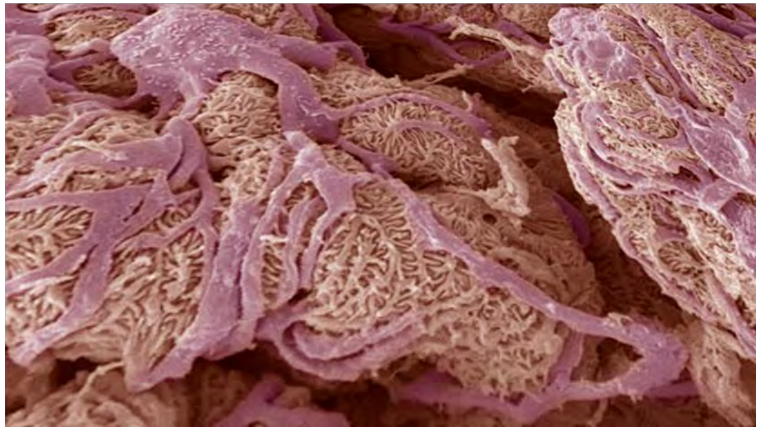
Electron microscopy, TEM



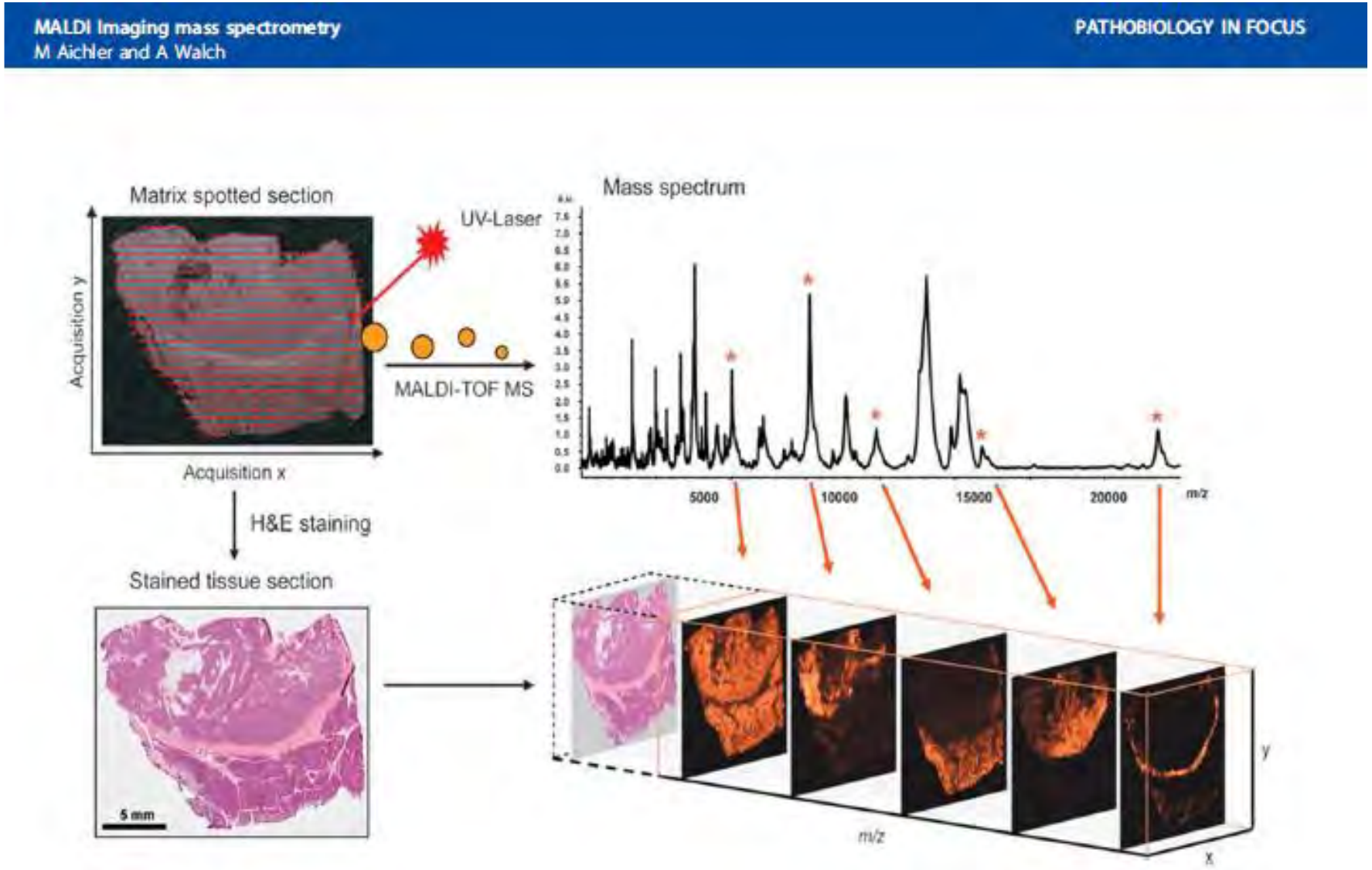
"Tissue microarrays" (TMA)



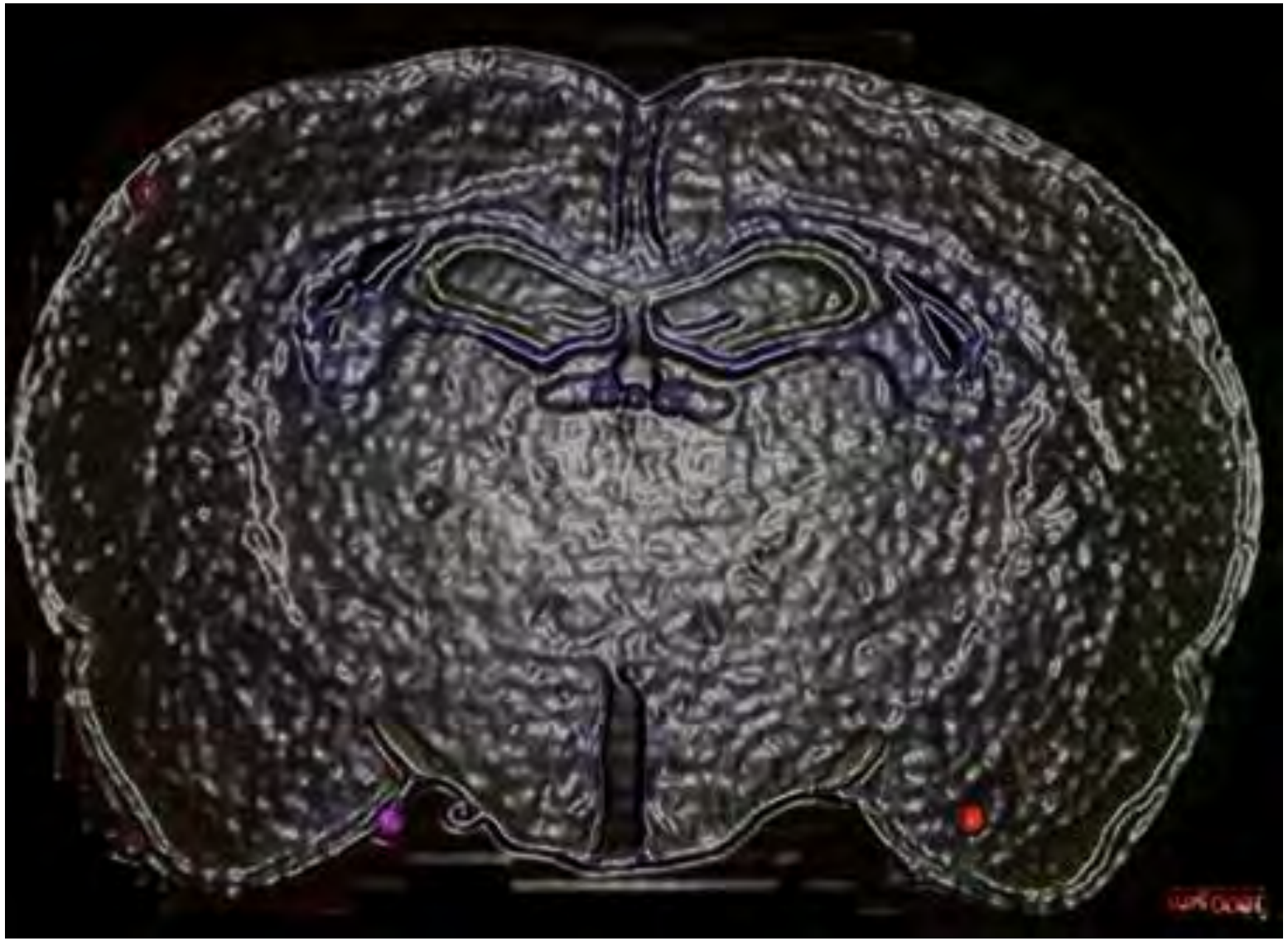
Electron microscopy, SEM



Imaging Mass Spectrometry



Analysis: What, where, how much, how many



"Diagnostic"

- Toxicologic studies

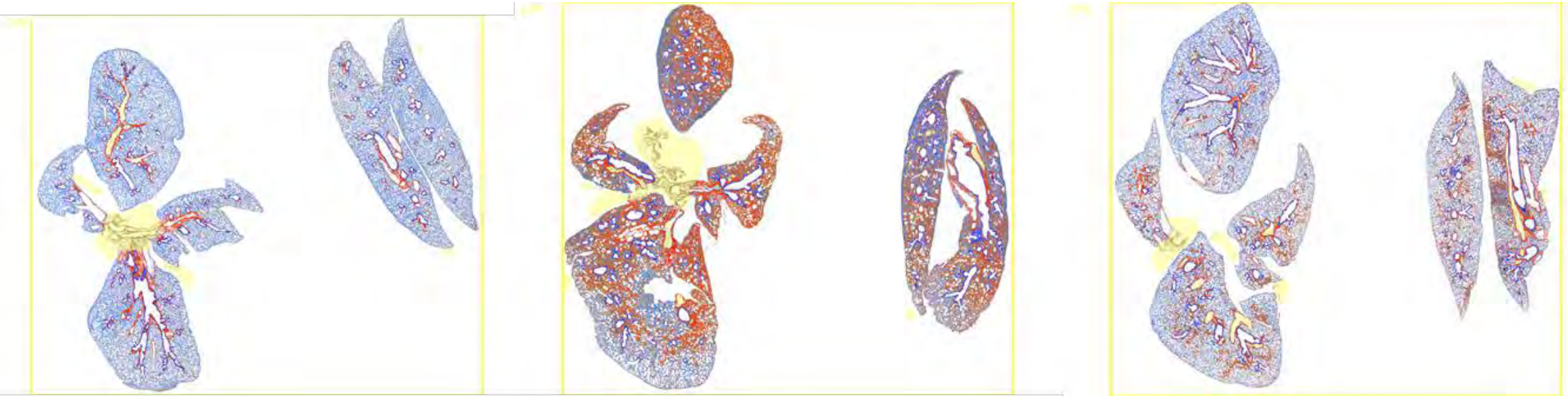
Descriptive: Where, what?

- Experimental pathology
- Toxicology studies

Semi-quantitative

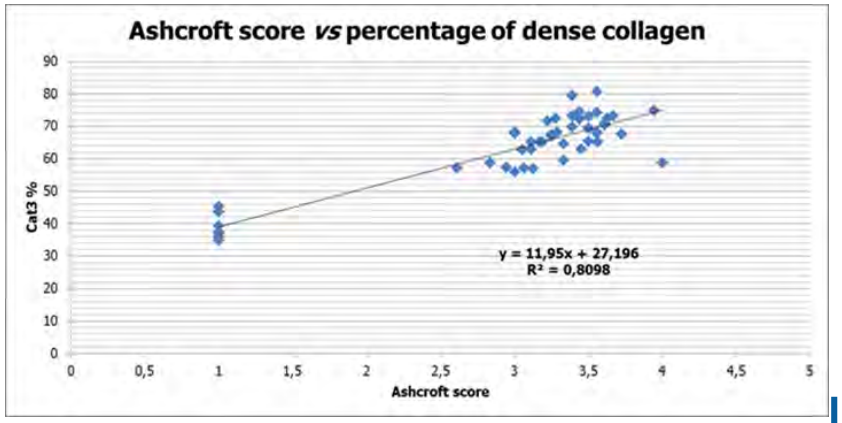
- Expression of results using predefined "categories"
  - "None-minimal-moderate-severe" for each category
- Median and range
- Non-parametric statistical methods

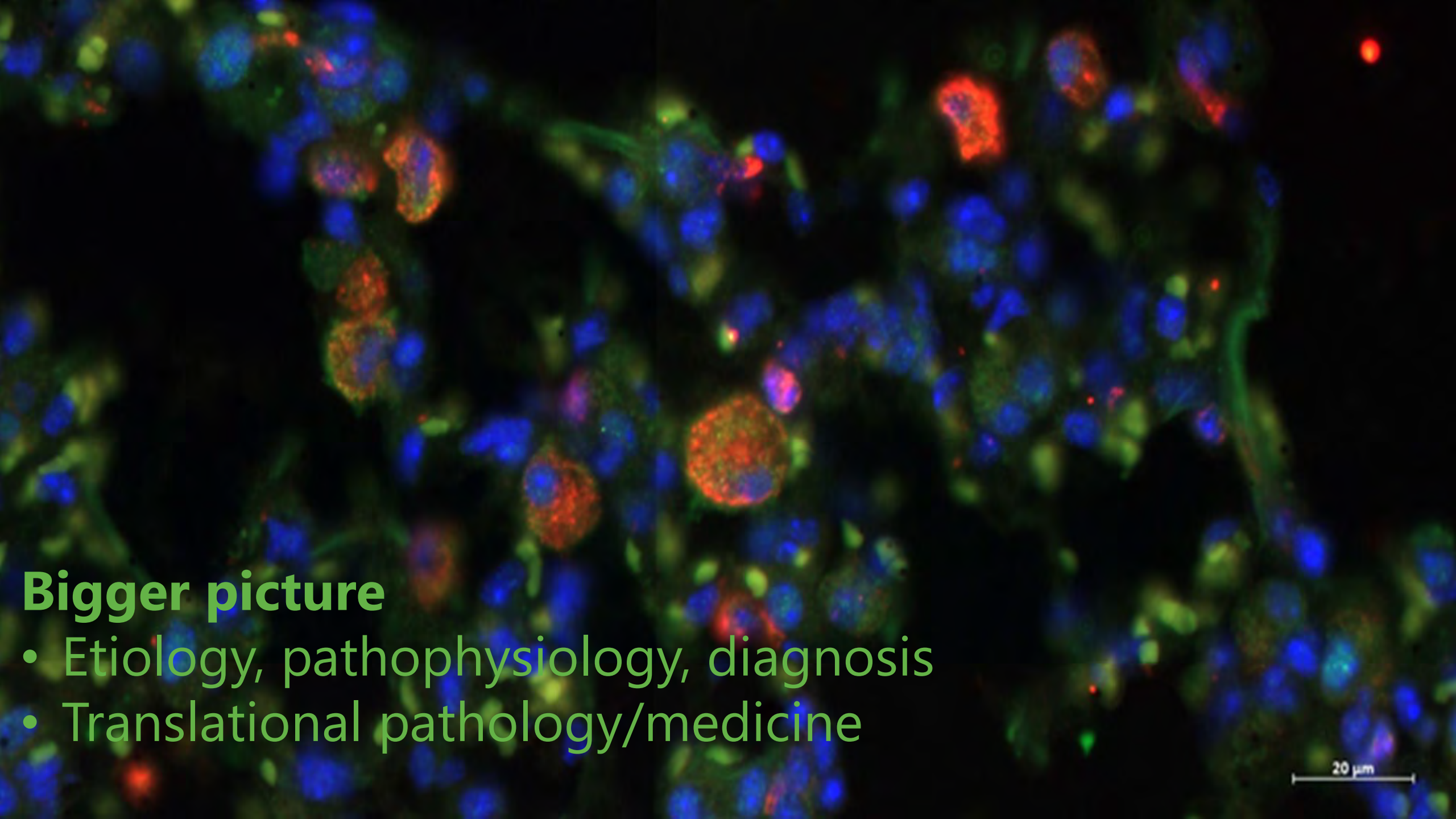
Analysis: What, where, how much, how many



Quantitative/Digital image analysis

- Numerical presentation of results
  - Number of mitoses/apoptoses, “positive” cells/ power field, mm^2, %
- Mean and standard deviation
- Parametric statistical methods





Bigger picture

- Etiology, pathophysiology, diagnosis
- Translational pathology/medicine

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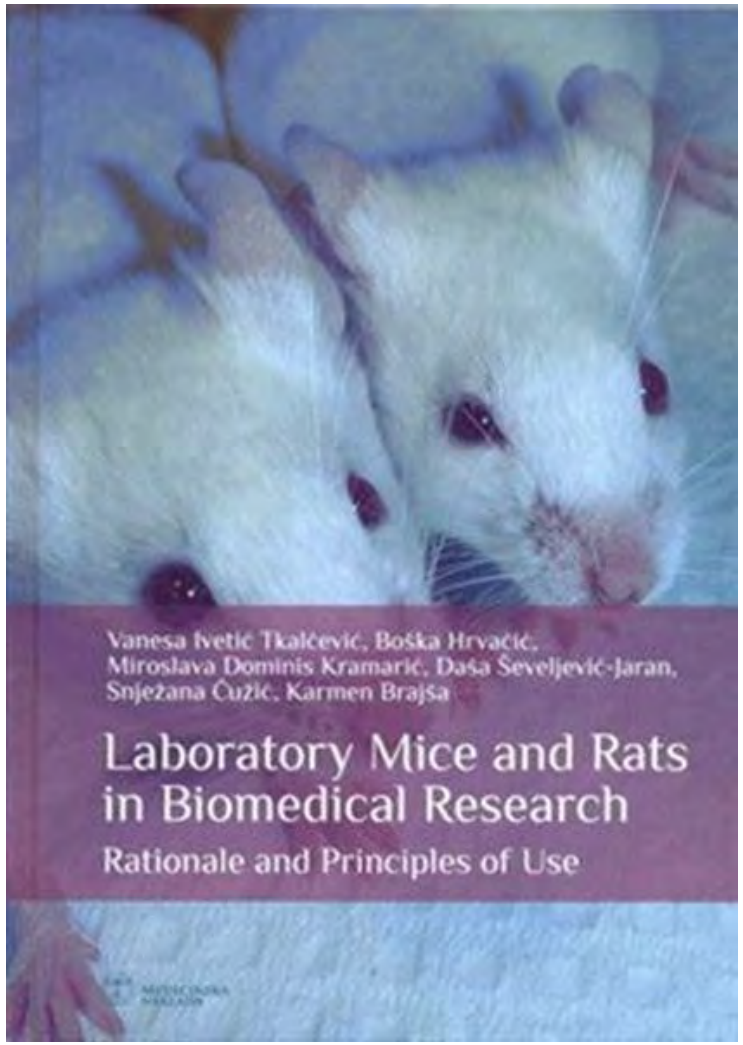
THANK YOU FOR ATTENTION!

Literature



Review

Evolving the Role of Discovery-focused Pathologists and Comparative Scientists in the Pharmaceutical Industry

Toxicologic Pathology
2019, Vol. 47(2) 121-128

DOI: 10.1177/0192623318821333
journals.sagepub.com/home/tpx
SAGE

Sunish Mohanan[1], Sean Maguire[1], Jan Klapwijk[2], Rick Adler[1], Richard Haworth[2], and Peter Clements[2]

Guidelines

ILAR Journal, 2019, 1–9
doi: 10.1093/ilar/ily020
Review Article

Pathology Study Design, Conduct, and Reporting to Achieve Rigor and Reproducibility in Translational Research Using Animal Models

Jeffrey I. Everitt[1], Piper M. Treuting[2], Cheryl Scudamore[3], Rani Sellers[4], Patricia V. Turner[5], Jerrold M. Ward[6], and Caroline J. Zeiss[7]

[1]Duke University, Durham, North Carolina, [2]University of Washington, Seattle, WA, [3]Envigo CRS Ltd, Huntingdon, UK, [4]Pfizer Inc., Pearl River, New York, [5]Department of Pathobiology, University of Guelph, Guelph, ON, Canada, [6]Global VetPathology, Montgomery Village, MD, and [7]Department of Comparative Medicine, Yale University School of Medicine, New Haven, Connecticut

ILAR Journal, 2018, 1–11
doi: 10.1093/ilar/ily008
Review Article

Selvita

Good Laboratory Practice in the Academic Setting: Fundamental Principles for Nonclinical Safety Assessment and GLP-Compliant Pathology Support When Developing Innovative Biomedical Products

Brad Bolon[1], Wallace Baze[2], Christopher J. Shilling[3], Kendy L. Keatley[4], Daniel J. Patrick[5], and Kenneth A. Schafer[6]

[1]GEMpath, Inc., Longmont, Colorado, [2]University of Texas MD Anderson Cancer Center, Michale E. Keeling Center for Comparative Medicine and Research, Department of Veterinary Sciences, Bastrop, Texas, [3]The Research Institute at Nationwide Children's Hospital, Center for Clinical and Translational Science, Drug and Device Development Services, Columbus, Ohio, [4]QA Consultant, Longmont, Colorado, [5]MPI Research, Mattawan, Michigan, and [6]Vet Path Services, Inc., Mason, Ohio

ILAR Journal, 2019, Vol. 59, No. 1, 1–3
doi: 10.1093/ilar/ilz008
Introduction

ILAR Journal, 2019, 1–5
doi: 10.1093/ilar/ily025
Review Article

An Introduction to Pathology in Biomedical Research: A Mission-Critical Specialty for Reproducibility and Rigor in Translational Research

Cory F. Brayton[1], Kelli L. Boyd[2], Jeffrey L. Everitt[3], David K. Meyerholz[4], Piper M. Treuting[5], and Brad Bolon[6]

[1]Department of Molecular and Comparative Pathobiology, Johns Hopkins University, School of Medicine, Baltimore, Maryland, [2]Department of Pathology Microbiology and Immunology, Vanderbilt University Medical Center, Nashville, Tennessee, [3]Department of Pathology, Duke University School of Medicine, Durham, North Carolina, [4]Department of Pathology, University of Iowa, Iowa City, Iowa, [5]Department of Comparative Medicine, University of Washington School of Medicine, Seattle, Washington, and [6]GEMpath Inc. Longmont, Colorado

Fundamental Concepts for Semiquantitative Tissue Scoring in Translational Research

David K. Meyerholz[1] and Amanda P. Beck[2]

[1]Department of Pathology, University of Iowa Carver College of Medicine, Iowa City, Iowa and [2]Department of Pathology, Albert Einstein College of Medicine, Bronx, New York

Guidelines

Exp Toxic Pathol 2003; 55: 91–106

Revised guides for organ sampling and trimming in rats and mice – Part 1

A joint publication of the RITA*) and NACAD) groups**

CHRISTINE RUEHL-FEHLERT[1], BIRGIT KITTEL[2], GERD MORAWIETZ[3], PAUL DESLEX[4], CHARLOTTE KEENAN[5], CHARLES R. MAHRT[6], THOMAS NOLTE[7], MERVYN ROBINSON[8], BARRY P. STUART[9], and ULRICH DESCHL[7]

Exp Toxic Pathol 2004; 55: 413–431

Revised guides for organ sampling and trimming in rats and mice – Part 2

A joint publication of the RITA*) and NACAD) groups**

BIRGIT KITTEL[1], CHRISTINE RUEHL-FEHLERT[2], GERD MORAWIETZ[3], JAN KLAPWIJK[4], MICHAEL R. ELWELL[5], BARBARA LENZ[6], M. GERARD O'SULLIVAN[7], DANIEL R. ROTH[8], and PETER F. WADSWORTH[9]

Exp Toxic Pathol 2004; 55: 433–449

Revised guides for organ sampling and trimming in rats and mice – Part 3

A joint publication of the RITA*) and NACAD) groups**

GERD MORAWIETZ[1], CHRISTINE RUEHL-FEHLERT[2], BIRGIT KITTEL[3], AXEL BUBE[4], KEVIN KEANE[5], SABINE HALM[6], ANKE HEUSER[7], and JÜRGEN HELLMANN[8]

Evolution of Quality Assurance for Clinical Immunohistochemistry in the Era of Precision Medicine: Part 1: Fit-for-Purpose Approach to Classification of Clinical Immunohistochemistry Biomarkers

Carol C. Cheung, MD, PhD, JD,†‡ Corrado D'Arrigo, MB, ChB, PhD, FRCPath,‡§‖ Manfred Dietel, MD, PhD,¶ Glenn D. Francis, MBBS, FRCPA, MBA, FFSc (RCPA),#,**,†† C. Blake Gilks, MD,‡‡ Jacqueline A. Hall, PhD,§§‖‖ Jason L. Hornick, MD, PhD,¶¶ Merdol Ibrahim, PhD,### Antonio Marchetti, MD, PhD,*** Keith Miller, FIBMS,### J. Han van Krieken, MD, PhD,††† Soren Nielsen, BMS,‡‡‡§§§ Paul E. Swanson, MD,‖‖‖ Clive R. Taylor, MD,¶¶¶ Mogens Vyberg, MD,‡‡‡§§§ Xiaoge Zhou, MD,####**** and Emina E. Torlakovic, MD, PhD,*†††‡‡‡‡ From the International Society for Immunohistochemistry and Molecular Morphology (ISIMM) and International Quality Network for Pathology (IQN Path)*

Evolution of Quality Assurance for Clinical Immunohistochemistry in the Era of Precision Medicine – Part 2: Immunohistochemistry Test Performance Characteristics

Emina E. Torlakovic, MD, PhD,†‡ Carol C. Cheung, MD, PhD, JD,*§ Corrado D'Arrigo, MB, ChB, PhD, FRCPath,‖¶§ Manfred Dietel, MD, PhD,** Glenn D. Francis, MBBS, FRCPA, MBA, FFSc (RCPA),††‡‡§§ C. Blake Gilks, MD,‖‖ Jacqueline A. Hall, PhD,¶¶ Jason L. Hornick, MD, PhD,### Merdol Ibrahim, PhD,*** Antonio Marchetti, MD, PhD,††† Keith Miller, FIBMS,*** J. Han van Krieken, MD, PhD,‡‡‡ Soren Nielsen, BMS,§§§‖‖‖ Paul E. Swanson, MD,¶¶¶ Mogens Vyberg, MD,§§§‖‖‖ Xiaoge Zhou, MD,####**** Clive R. Taylor, MD,†††† and From the International Society for Immunohistochemistry and Molecular Morphology (ISIMM) and International Quality Network for Pathology (IQN Path)*

Evolution of Quality Assurance for Clinical Immunohistochemistry in the Era of Precision Medicine. Part 3: Technical Validation of Immunohistochemistry (IHC) Assays in Clinical IHC Laboratories

Emina E. Torlakovic, MD, PhD,†‡ Carol C. Cheung, MD, PhD, JD,*§ Corrado D'Arrigo, MB, ChB, PhD, FRCPath,‖¶§ Manfred Dietel, MD, PhD,** Glenn D. Francis, MBBS, FRCPA, MBA, FFSc (RCPA),††‡‡§§ C. Blake Gilks, MD,‖‖ Jacqueline A. Hall, PhD,¶¶ Jason L. Hornick, MD, PhD,### Merdol Ibrahim, PhD,*** Antonio Marchetti, MD, PhD,††† Keith Miller, FIBMS,*** J. Han van Krieken, MD, PhD,‡‡‡ Soren Nielsen, BMS,§§§‖‖‖ Paul E. Swanson, MD,¶¶¶ Mogens Vyberg, MD,§§§‖‖‖ Xiaoge Zhou, MD,####**** and Clive R. Taylor, MD,†††† From the International Society for Immunohistochemistry and Molecular Morphology (ISIMM) and International Quality Network for Pathology (IQN Path)*

Evolution of Quality Assurance for Clinical Immunohistochemistry in the Era of Precision Medicine: Part 4: Tissue Tools for Quality Assurance in Immunohistochemistry

Carol C. Cheung, MD, PhD, JD,†‡ Corrado D'Arrigo, MB, ChB, PhD, FRCPath,‡§‖ Manfred Dietel, MD, PhD,¶ Glenn D. Francis, MBBS, FRCPA, MBA, FFSc (RCPA),#,**,†† Regan Fulton, MD, PhD,‡‡ C. Blake Gilks, MD,§§ Jacqueline A. Hall, PhD,‖‖¶¶ Jason L. Hornick, MD, PhD,### Merdol Ibrahim, PhD,*** Antonio Marchetti, MD, PhD,†††‡‡‡ Keith Miller, FIBMS,*** J. Han van Krieken, MD, PhD,§§§ Soren Nielsen, BMS,‖‖‖¶¶¶ Paul E. Swanson, MD,#### Clive R. Taylor, MD,**** Mogens Vyberg, MD,‖‖‖¶¶¶ Xiaoge Zhou, MD,††††‡‡‡‡ Emina E. Torlakovic, MD, PhD,*§§§‖‖‖ and From the International Society for Immunohistochemistry and Molecular Morphology (ISIMM) and International Quality Network for Pathology (IQN Path)*

Appl Immunohistochem Mol Morphol (2017) Volume 1-4

Database

https://www.jax.org/news-and-insights/jax-blog/2018/april/the-mouse-tumor-biology-database

https://www.ebi.ac.uk/gxa/home

http://www.pathbase.net/

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https://ntp.niehs.nih.gov/whoweare/about/index.html

https://embryology.med.unsw.edu.au/embryology/index.php/Main_Page

https://mouse.brain-map.org/experiment/thumbnails/100142144?image_type=atlas

http://www.drjastrow.de/EMAtlasE.html

https://reni.item.fraunhofer.de/reni/trimming/index.php

https://www.goreni.org/

https://reni.item.fraunhofer.de/reni/public/rita/index.php