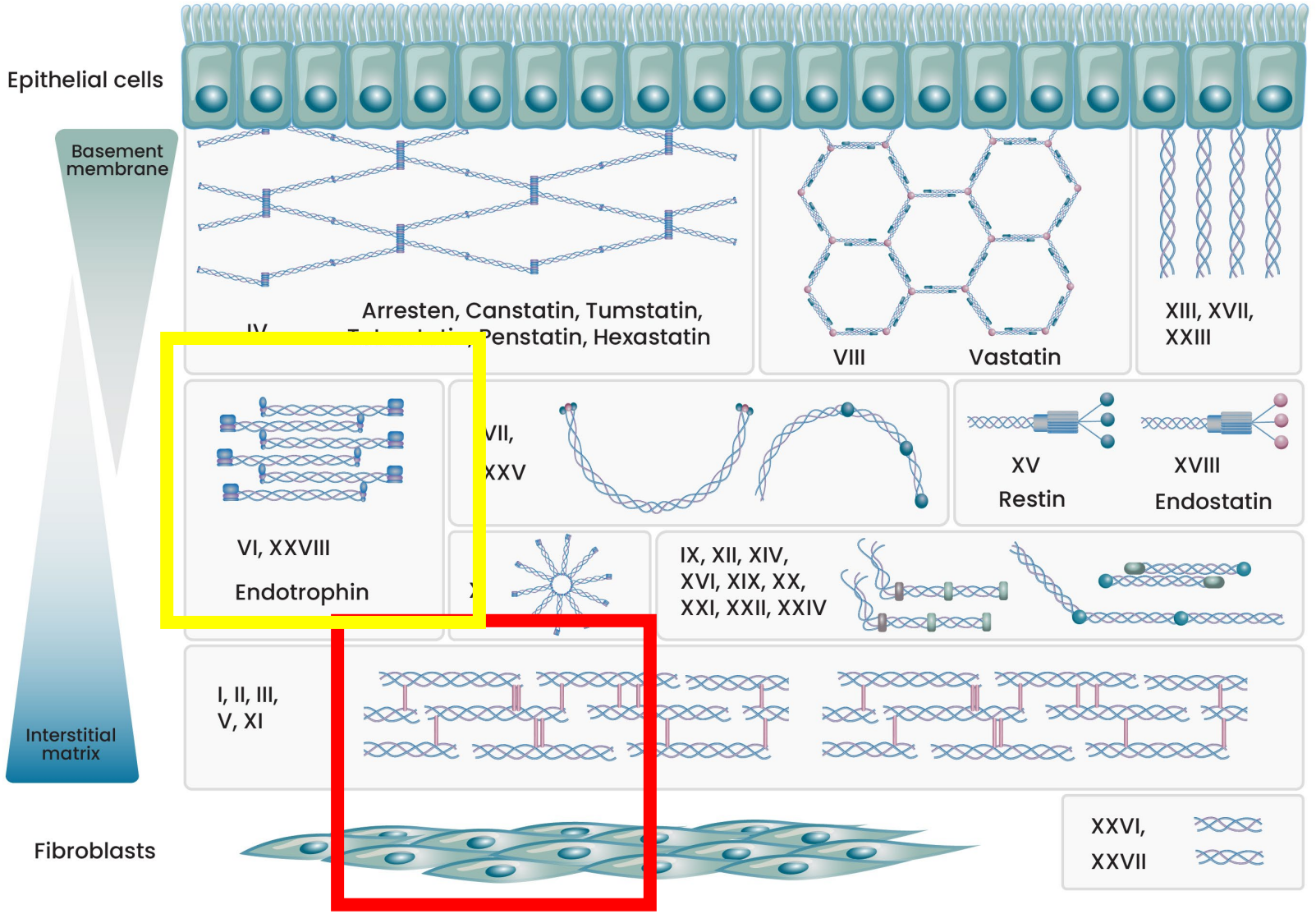
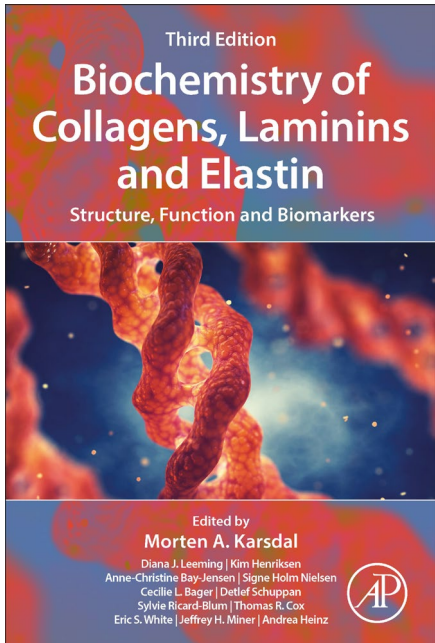
NORDIC BIOSCIENCE

Fibroblast activities are related to outcome in PSC – a target to treat

NORDIC BIOSCIENCE

The 28 (46) collagens; Structure, function and positon in a healthy tissue





NORDIC BIOSCIENCE

Fibroblast and fibrillar collagen over growth

Journal of Pathology
J Pathol January 2024; **262:** 22–36
Published online 20 September 2023 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/path.6207

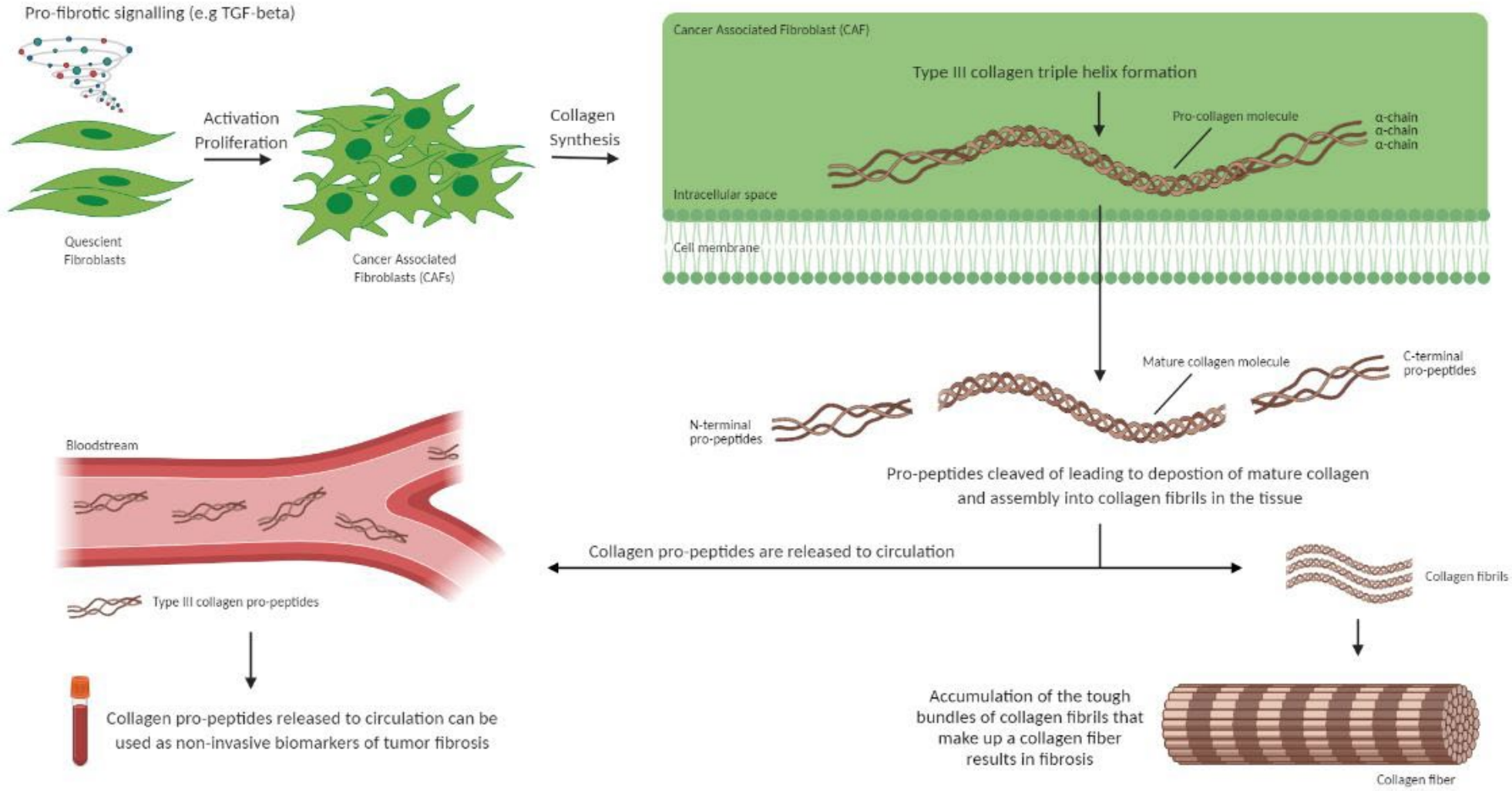
ORIGINAL ARTICLE

The collagen landscape in cancer: profiling collagens in tumors and in circulation reveals novel markers of cancer-associated fibroblast subtypes

Jeppe Thorlacius-Ussing[1,2*], Christina Jensen[2], Neel I Nissen[2], Thomas R Cox[3,4], Raghu Kalluri[5], Morten Karsdal[2] and Nicholas Willumsen[2]

[1] *Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, København N, Denmark*
[2] *Biomarkers & Research, Nordic Bioscience A/S, Herlev, Denmark*
[3] *Matrix and Metastasis Lab, Cancer Ecosystems Program, Garvan Institute of Medical Research and The Kinghorn Cancer Centre, Darlinghurst, NSW, Australia*
[4] *School of Clinical Medicine, UNSW Medicine & Health, UNSW Sydney, Sydney, NSW, Australia*
[5] *Department of Cancer Biology, University of Texas MD Anderson Cancer Center, Houston, TX, USA*

The type III collagen production and epitope



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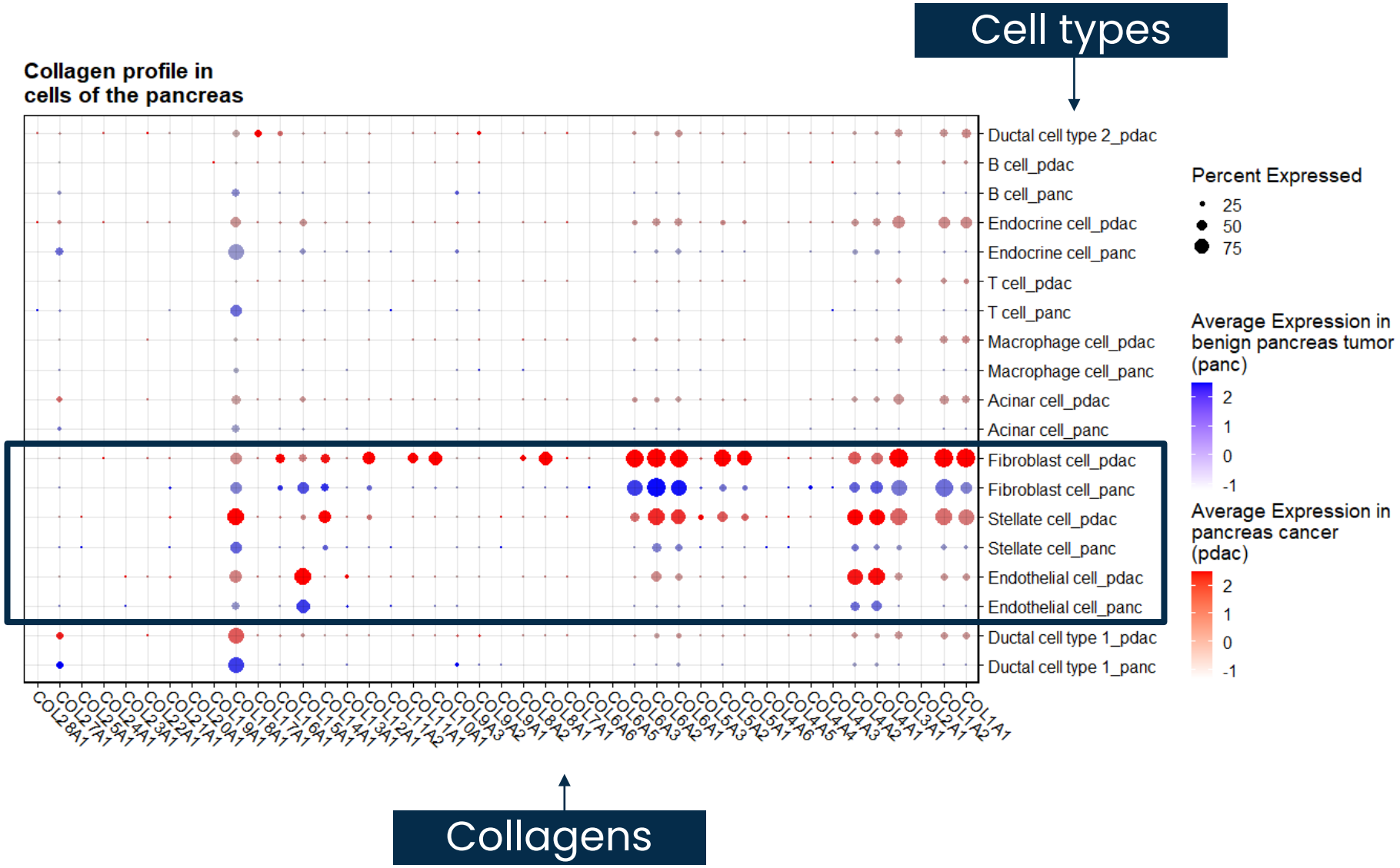
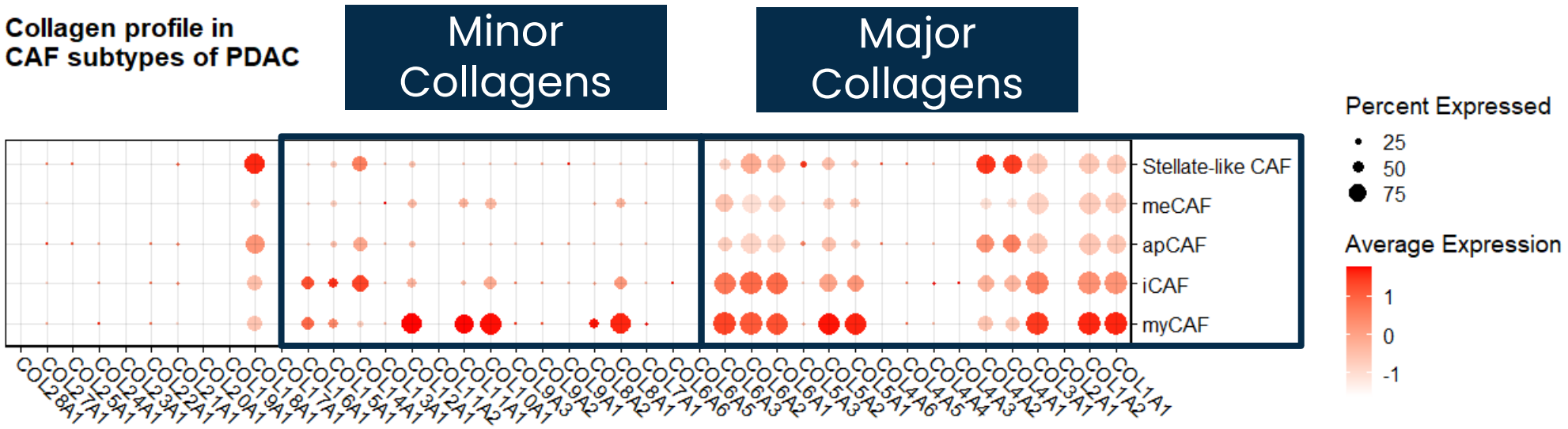
Fibroblast and stellate cells produce the collagens



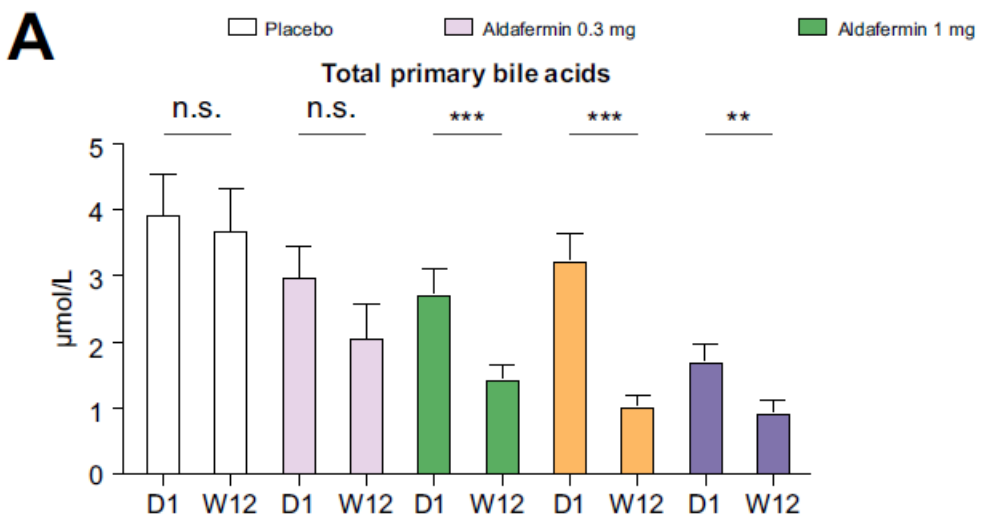
NORDIC BIOSCIENCE

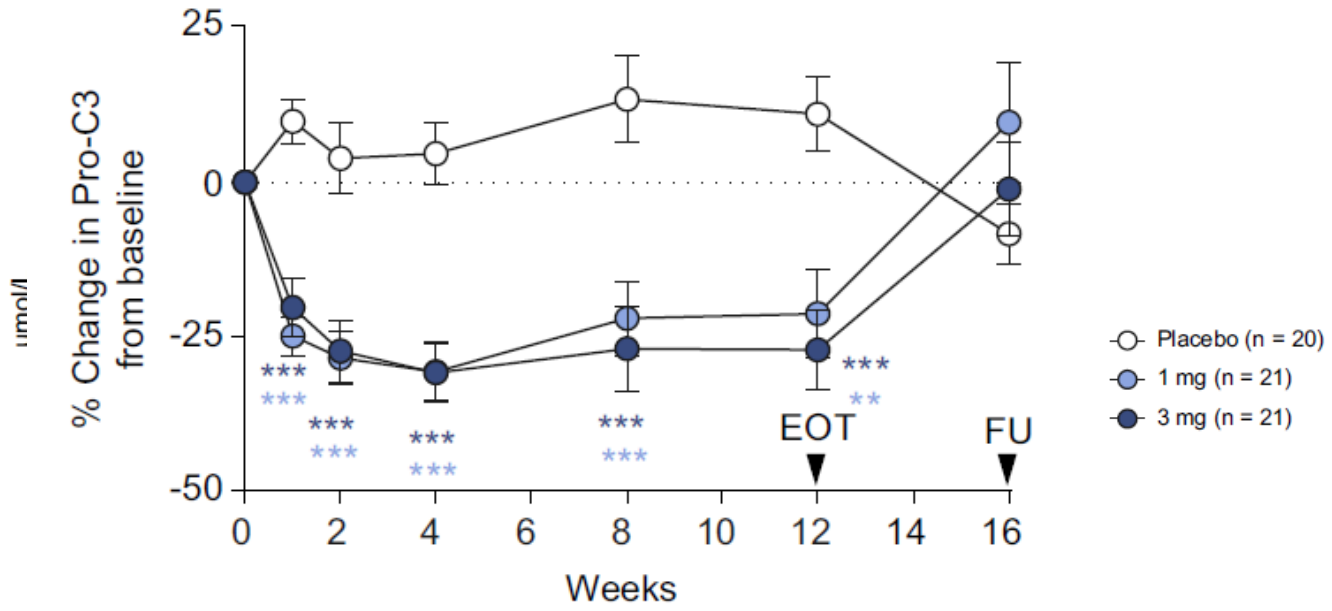
Minor collagens more specific to myCAF subtypes



Thorlacius-Ussing, 2023

ELF & PRO-C3 are dynamically modulated by Aldafermin - Pharmacodynamic



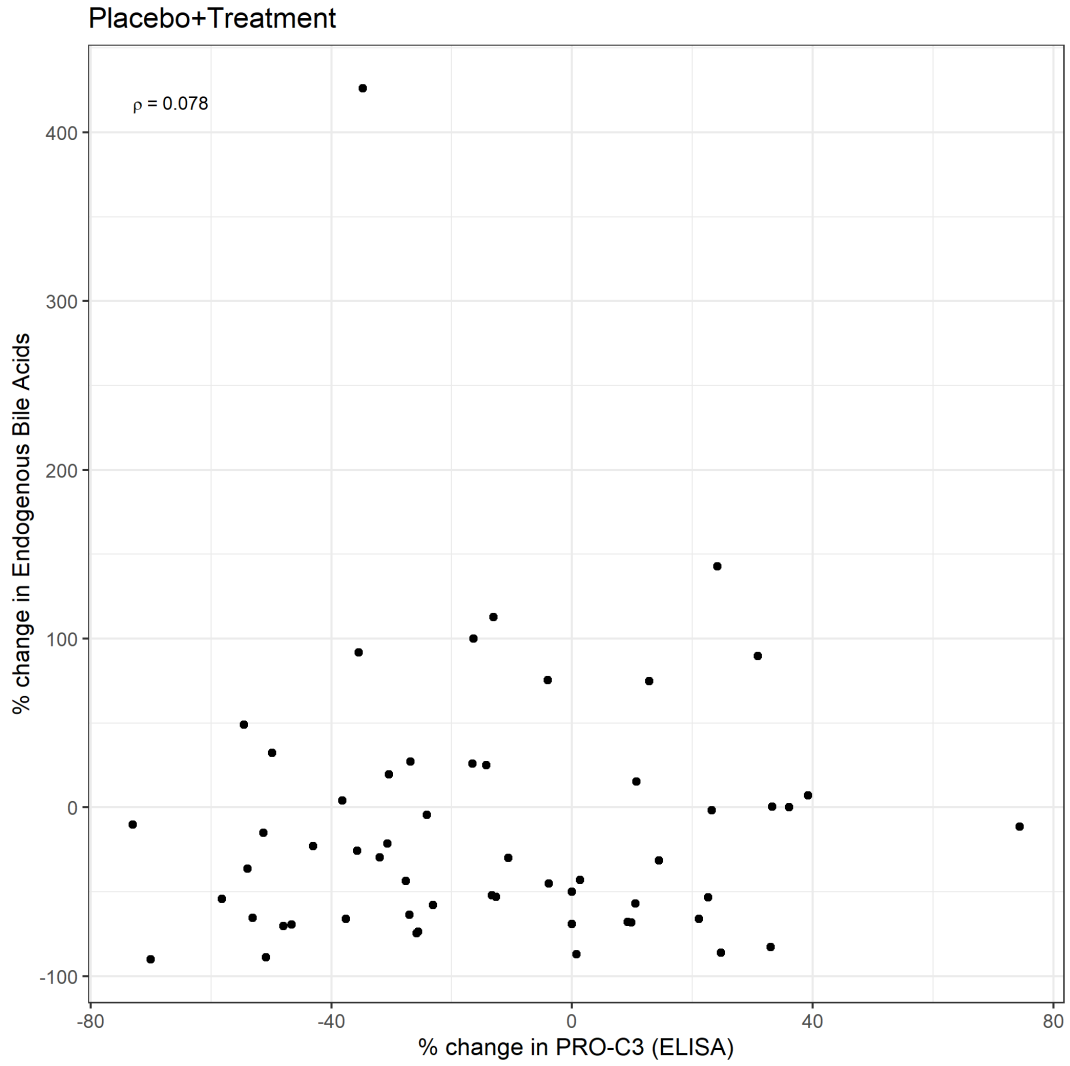


PL n=20; 1mg: n=21; 2mg n=21

Arun Sanyak & Hirschfield G et al , Journal of Hepatology 2018

NORDIC BIOSCIENCE

Endogenous bile acids vs. PRO-C3 (ELISA)



Correlation of bile acid versus PRO-C3 (PSC)

Serum Bile Acids Correlate with Pro-C3

- Serum concentrations of individual bile acids, and conjugated primary bile acids in particular, significantly correlated with Pro-C3
- The lack of correlation of serum bile acids with C4 likely reflects the adaptive suppression of de novo bile acid synthesis in cholestasis in this patient population

Week 12	Pro-C3		C4	
	P value	P value	r value	P value
Conjugated primary bile acids				
GCA	0.62	<0.0001	−0.03	0.83
TCA	0.52	<0.0001	−0.12	0.37
GCDCA	0.55	<0.0001	−0.25	0.06
TCDCA	0.46	0.0003	−0.28	0.032
Conjugated secondary bile acids				
GDCA	0.31	0.020	0.27	0.038
TDCA	0.28	0.038	0.22	0.09
Unconjugated primary bile acids				
CA	−0.18	0.18	0.09	0.49
CDCA	−0.21	0.12	−0.01	0.92
Unconjugated secondary bile acids				
DCA	−0.06	0.65	0.52	<0.0001

Delta GCA versus delta PRO-C3

Potent suppression of hydrophobic bile acids by aldafermin, an FGF19 analogue, across metabolic and cholestatic liver diseases

Authors
Arun J. Sanyal, Lei Ling, Ulrich Beuers, Alex M. DePaoli, Hsiao D. Lieu, Stephen A. Harrison, Gideon M. Hirschfield
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lling@ngmbio.com (L. Ling), arun.sanyal@vcuhealth.org (A.J. Sanyal).

Graphical abstract

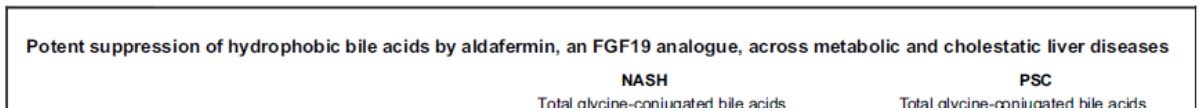


Table 3. Correlation between changes in bile acids and changes in Pro-C3 in the pooled NASH and PSC populations.

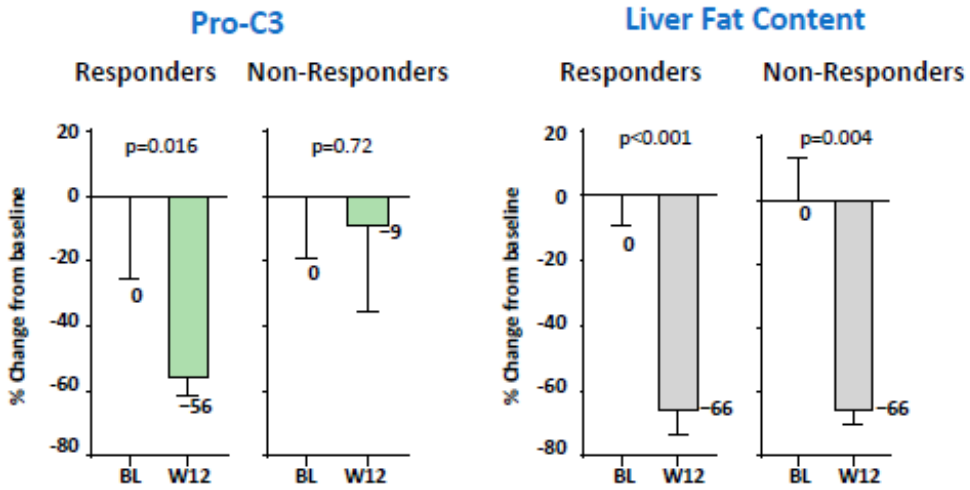
Percent change in bile acids from baseline to week 12	Percent change in Pro-C3 from baseline to week 12	
	rho	*p* value
Primary bile acids		
Glycine-conjugated primary bile acids		
GCA (μmol/L)	0.33	<0.001
GCDCA (μmol/L)	0.25	<0.001
Taurine-conjugated primary bile acids		
TCA (μmol/L)	0.16	0.02
TCDCA (μmol/L)	0.06	0.38
Unconjugated primary bile acids		
CA (μmol/L)	0.23	0.001
CDCA (μmol/L)	0.17	0.01
Secondary bile acids		
Glycine-conjugated secondary bile acids		
GDCA (μmol/L)	0.34	<0.001
GLCA (μmol/L)	0.30	<0.001
Taurine-conjugated secondary bile acids		
TDCA (μmol/L)	0.31	<0.001
TLCA (μmol/L)	-0.01	0.86
Unconjugated secondary bile acids		
DCA (μmol/L)	0.36	<0.001
LCA (μmol/L)	0.30	<0.001

Data are presented as correlation coefficients. Values of *p* by Spearman's method. CA, cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; GCA, glycocholic acid; GCDCA, glycochenodeoxycholic acid; GDCA, glycodeoxycholic acid; GLCA, glycolithocholic acid; LCA, lithocholic acid; TCA, taurocholic acid; TCDCA, taurochenodeoxycholic acid; TDCA, taurodeoxycholic acid; TLCA, taurolithocholic acid.

Change in bile acid versus PRO-C3 (NASH)

Greater Reductions in Pro-C3 in Histological Responders

- In a histology cohort of patients receiving NGM282 3 mg for 12 weeks with paired biopsies, 63% of the patients improved NAS by two or more points without fibrosis worsening, and 42% of the patients improved liver fibrosis by one stage or more without worsening of steatohepatitis [6]
- Greater reductions in Pro-C3, but not in liver fat content, were observed in histological responders (improve NAS ≥2 or fibrosis ≥1) than in non-responders



NORDIC BIOSCIENCE

Baseline demographics – PSC

Received: 4 January 2018 | First decision: 21 January 2018 | Accepted: 24 April 2018

DOI: 10.1111/apt.14806

WILEY APT Alimentary Pharmacology & Therapeutics

Serological markers of extracellular matrix remodeling predict transplant-free survival in primary sclerosing cholangitis

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Study Intro PSC & UC cohort

Table 1. Baseline Characteristics of Primary Sclerosing Cholangitis (PSC) Patients

	Derivation Panel			Validation Panel		
	Transplantation-Free Survivors	Transplantation/ Death	*P*	Transplantation-Free Survivors	Transplantation/ Death	*P*
n	52	115		91	47	
Males, n (%)	38 (73.1)	86 (74.8)	NS	73 (80.2)	34 (72.3)	NS
Mean age, years (95% CI)	35.1 (31.4-38.8)	42.2 (39.8-44.6)	0.002	38.1 (35.4-40.9)	47.7 (44.1-51.2)	<0.001
Age at diagnosis, years, median (range)	32.2 (13.8-70.1)	35.1 (13.2-70.0)	NS	31.0 (14.5-65.8)	42.9 (20.7-71.5)	0.001
PSC duration, years, median (range)	0.2 (0-20.9)	2.9 (−0.2 to 22.4)	<0.001	0.6 (−0.6 to 29.0)	3.2 (0-26.5)	0.039
IBD ever, n (%)*	41 (87.2)	98 (89.9)	NS	70 (87.8)	32 (68.1)	NS
Time of follow-up, years, median (range)	11.8 (7.2-20.1)	1.4 (0-17.5)	<0.001	2.8 (0.53-4.29)	0.4 (0-3.9)	<0.001
Liver transplant, n (%)	0	85 (73.9)		0	33 (70.2)	
Death as endpoint, n (%)	0	30 (26.1)		0	14 (29.8)	
Mayo risk score, median (range)*	−0.17 (−2.24 to 2.91)	1.44 (−1.39 to 5.26)	<0.001	−0.24 (−2.37 to 3.20)	1.40 (−0.95 to 4.13)	<0.001
Laboratory data						
ALP, U/L, median (range)*	413 (124-1883)	741 (70-3100)	0.022	204 (51-1459)	314 (82-892)	<0.001
ALP, by ULN, median (range)*	2.5 (0.5-9.3)	3.5 (0.7-15.9)	0.003	1.9 (0.5-13.9)	3.0 (0.8-8.5)	<0.001
AST, U/L, median (range)*	57 (8-556)	108 (10-1012)	0.009	56 (16-1219)	100 (32-585)	<0.001
ALT, U/L, median (range)*	110 (9-780)	108.5 (8-524)	NS	74 (14-885)	99 (22-768)	NS
Albumin, g/L, median (range)*	40 (22-50)	34 (15-46)	<0.001	42 (28-50)	37 (23-46)	<0.001
Total bilirubin, µmol/L, median (range)*	16 (5-227)	54 (5-567)	<0.001	13 (3-175)	46 (5-532)	<0.001
Creatinine, µmol/L, median (range)*	73.5 (51-98)	73 (41-216)	NS	67 (39-91)	61 (37-111)	NS
Platelets, 10^9/L, median (range)*	256 (10-756)	223 (35-879)	0.008	290 (65-903)	277 (22-759)	NS

*Refers to subpopulations of (1) derivation panel transplant-free survivors, n = 44-49; (2) derivation panel transplantation/death, n = 81-109; (3) validation panel transplant-free survivors, n = 83-90; (4) validation panel transplantation/death, n = 45-47.

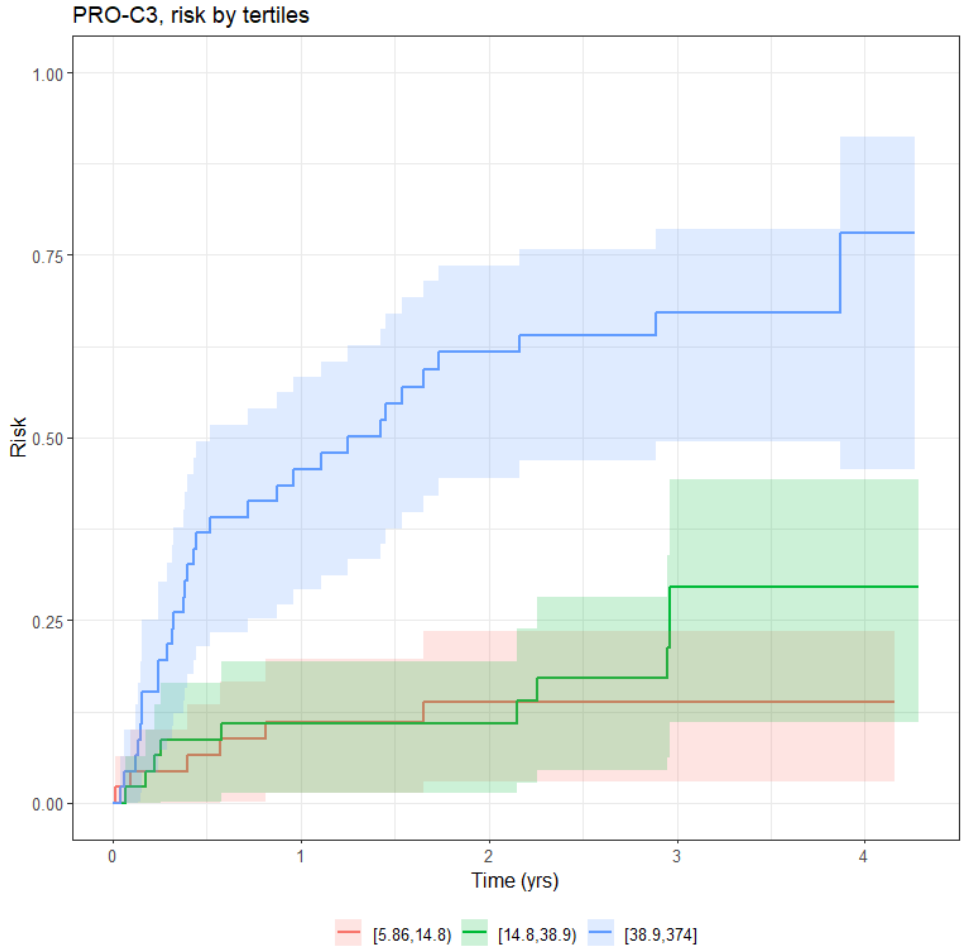
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IBD, inflammatory bowel disease; NS, not significant ($P \geq 0.05$); ULN upper limit of normal.

Vesterhus et al. "Enhanced liver fibrosis score predicts transplant-free survival in primary sclerosing cholangitis." *Hepatology* 62.1 (2015): 188-197.

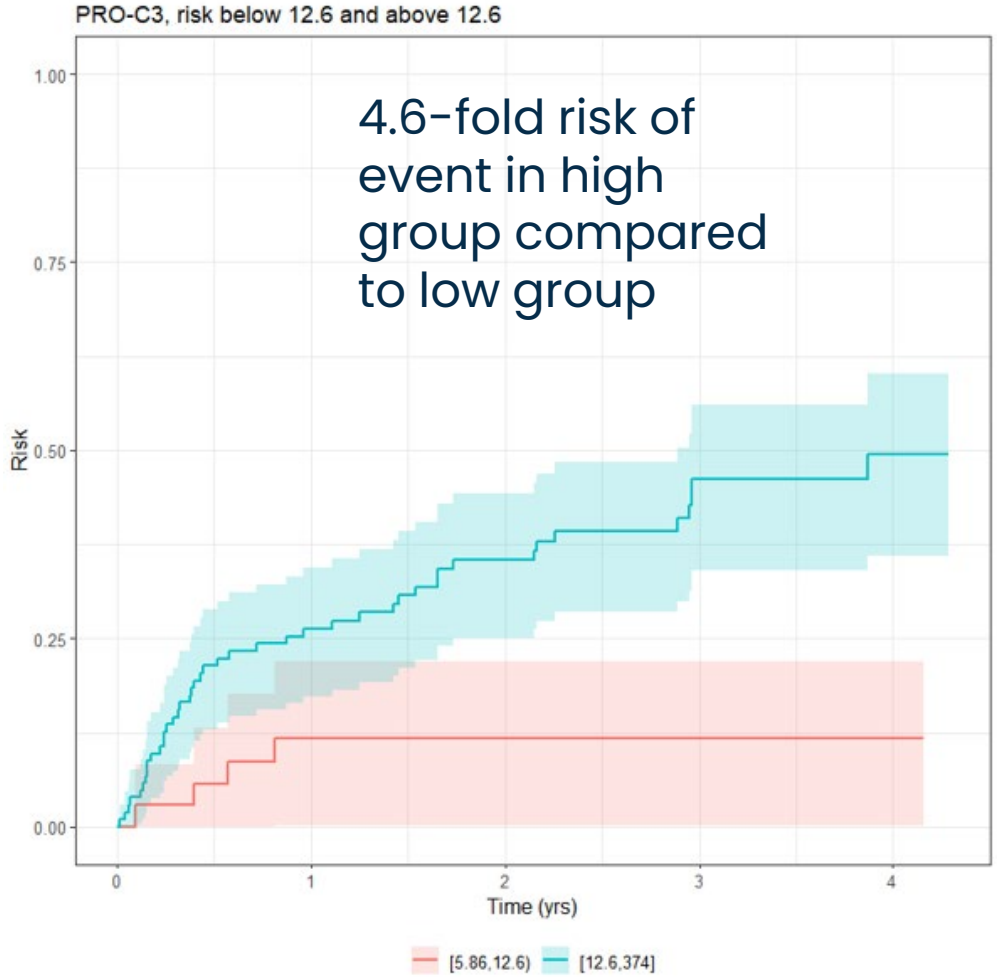
167 well characterized large duct PSC patients (4 years follow up)

PSC diagnosis - typical cholangiographic findings by MR cholangiopancreatography or endoscopic retrograde cholangiopancreatography

PRO-C3 risk – 8 fold risk of an outcome !



Tertile	n	Median	Min	Max
[5.86,14.8)	46	10.8	5.9	14.6
[14.8,38.9)	46	24.8	14.9	38.8
[38.9,374]	46	67.1	39.3	374.4



PRO-C3, 4 yr risk

Group	n	Median	Min	Max
[5.86,12.7)	36	9.9	5.9	12.7
[12.7,374]	102	35.8	13.3	374.4

Group	Risk [95% CI]
[5.86,12.7)	0.11 [0.00, 0.21]
[12.7,374]	0.50 [0.36, 0.60]

Aldafermin paper 2018

Research Article
Cholestasis and Autoimmune Diseases

JOURNAL
OF HEPATOLOGY

Effect of NGM282, an FGF19 analogue, in primary sclerosing cholangitis: A multicenter, randomized, double-blind, placebo-controlled phase II trial

Gideon M. Hirschfield[1,2,3,4,*], Olivier Chazouillères[5], Joost P. Drenth[6], Douglas Thorburn[7], Stephen A. Harrison[8], Charles S. Landis[9], Marlyn J. Mayo[10], Andrew J. Muir[11], James F. Trotter[12], Diana J. Leeming[13], Morten A. Karsdal[13], Mark J. Jaros[14], Lei Ling[15], Kathline H. Kim[15], Stephen J. Rossi[15], Ransi M. Somaratne[15], Alex M. DePaoli[15], Ulrich Beuers[16]

[1]National Institute for Health Research (NIHR) Birmingham Biomedical Research Centre, Birmingham, United Kingdom; [2]University Hospitals Birmingham, Birmingham, United Kingdom; [3]Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, United Kingdom; [4]Toronto Centre for Liver Disease, University Health Network, University of Toronto, Toronto, Canada; [5]Reference Center for Inflammatory Biliary Diseases and Autoimmune Hepatitis, Hepatology and Gastroenterology Department, Saint-Antoine University Hospital, Assistance Publique-Hopitaux de Paris, and INSERM UMR S938, Sorbonne University, Paris, France; [6]Department of Gastroenterology and Hepatology, Radboud UMC, Nijmegen, the Netherlands; [7]Sheila Sherlock Liver Centre and UCL Institute of Liver and Digestive Health, Royal Free Hospital, London, United Kingdom; [8]University of Oxford, Oxford, United Kingdom; [9]Division of Gastroenterology and Hepatology, University of Washington, Seattle, United States; [10]University Texas Southwestern Medical Center, Dallas, United States; [11]Division of Gastroenterology, Department of Medicine, Duke University, Durham, United States; [12]Texas Digestive Disease Consultants, Clinical Research, Southlake, United States; [13]Nordic Bioscience, Herlev, Denmark; [14]Summit Analytical, Denver, United States; [15]NGM Biopharmaceuticals, South San Francisco, United States; [16]Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands

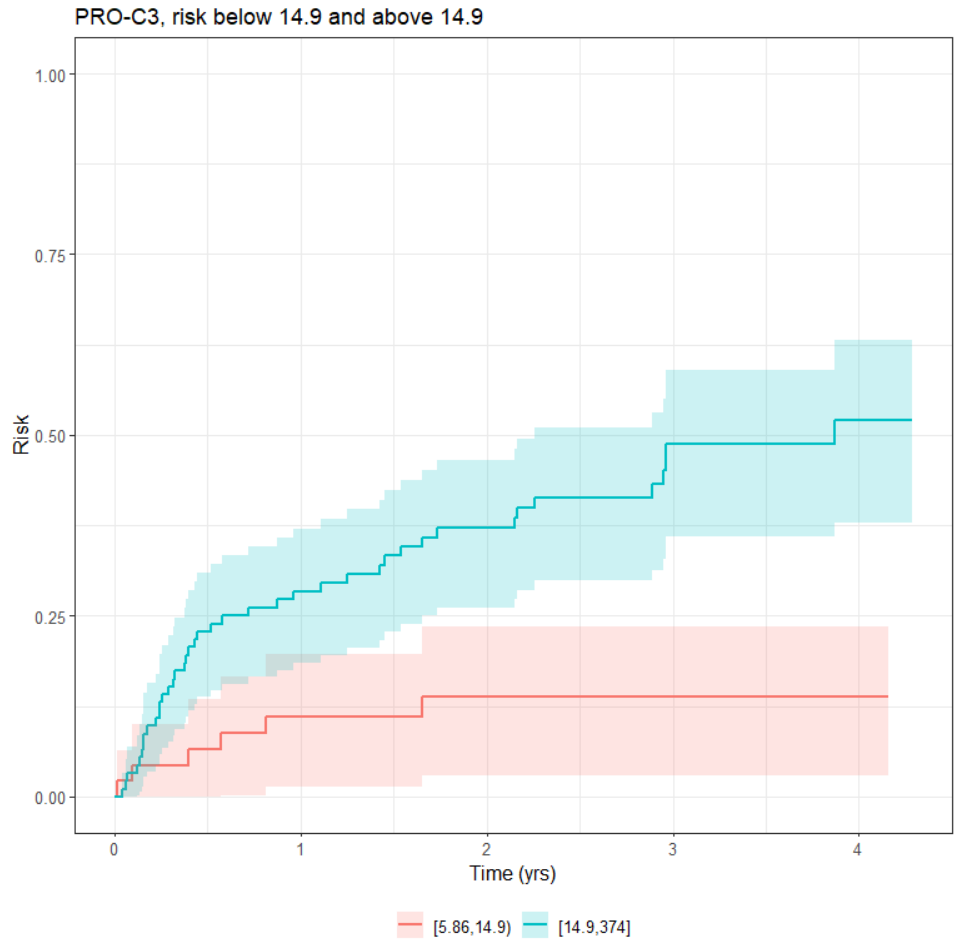
PRO-C3 levels in Aldafermin phase 2

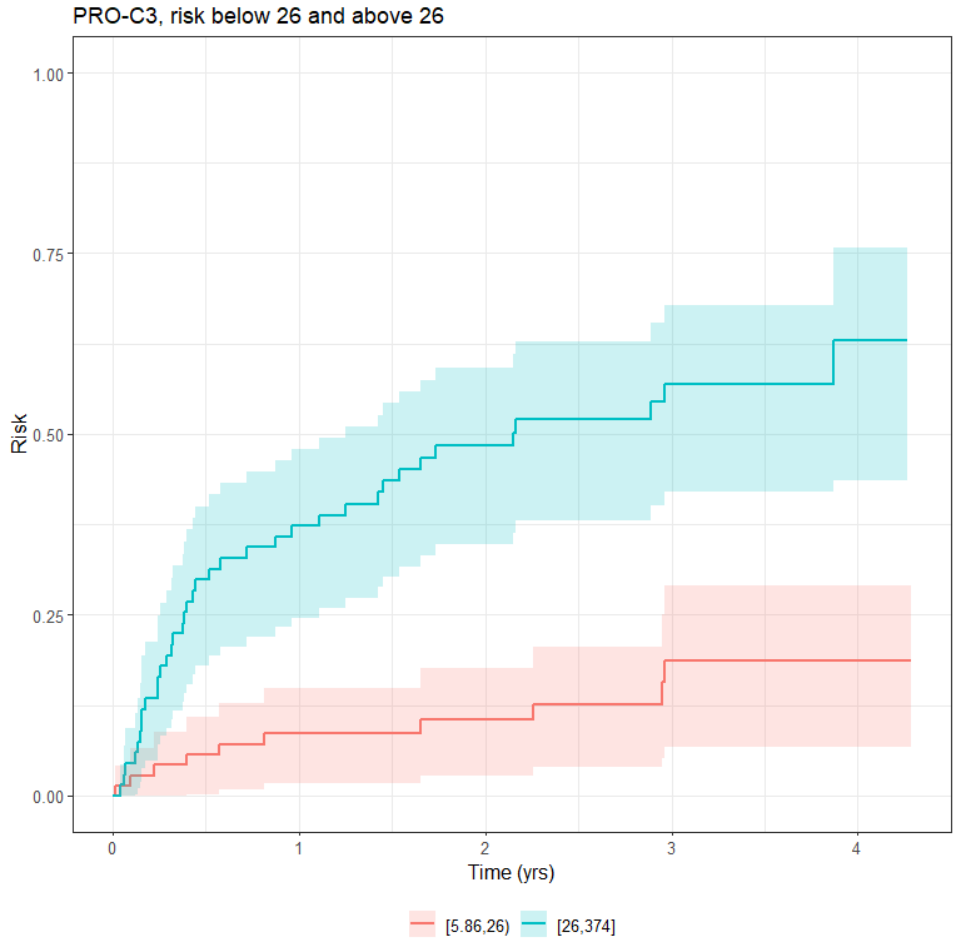
Table 1. Baseline patient demographics and characteristics.

	Placebo (n = 20)	NGM282 1 mg (n = 21)	NGM282 3 mg (n = 21)
Mean age, years	43.4 ± 12.4	46.0 ± 15.9	40.2 ± 13.0
Male, n (%)	12 (60)	14 (67)	12 (57)
Female, n (%)	8 (40)	7 (33)	9 (43)
Duration of PSC, years	8.1 ± 7.2	7.3 ± 6.1	7.8 ± 7.6
Race, n (%)			
Asian	0	1 (5)	0
Black	4 (20)	1 (5)	2 (10)
White	16 (80)	18 (86)	18 (86)
Other	0	1 (5)	1 (5)
Ethnic origin, n (%)			
Hispanic/Latino	0	1 (5)	0
UDCA status, n (%)			
Concomitant UDCA	13 (65)	13 (62)	13 (62)
No concomitant UDCA	7 (35)	8 (38)	8 (38)
Cholangiography by MRCP or ERCP, n (%)			
Large duct PSC	13 (65)	10 (48)	14 (67)
Dominant stricture	5 (25)	2 (10)	3 (14)
Bile acid-related			
C4 (ng/ml)	10.5 ± 11.2	12.9 ± 12.8	16.9 ± 18.2
C4 ≤2 ng/ml	5 (25)	4 (19)	4 (19)
Endogenous bile acids (μmol/L)	30.2 ± 33.0	39.1 ± 42.4	20.1 ± 32.0
Endogenous FGF19 (pg/ml)	433.3 ± 339.1	339.7 ± 279.5	305.8 ± 241.1
Serum liver tests			
Alkaline phosphatase (U/L)	355.5 ± 137.9	383.2 ± 181.4	353.7 ± 194.0
Alanine aminotransferase (U/L)	90.5 ± 51.8	116.7 ± 70.2	96.1 ± 67.3
Aspartate aminotransferase (U/L)	71.1 ± 36.9	92.6 ± 59.7	70.3 ± 46.4
Total bilirubin (μmol/L)	12.1 ± 6.0	17.9 ± 8.4	10.7 ± 4.3
Fibrosis biomarkers			
Pro-C3 (ng/ml)	26.1 ± 16.4	26.7 ± 17.9	24.2 ± 16.7
Pro-C3 ≥ 20 ng/ml	12 (60)	10 (48)	10 (48)
ELF score	10.0 ± 1.4	10.2 ± 1.2	9.5 ± 1.1
Hyaluronic acid (μg/L)	160.8 ± 261.6	203.8 ± 488.7	60.1 ± 60.2
PIIINP (μg/L)	14.2 ± 8.3	13.9 ± 6.3	12.6 ± 4.2
TIMP-1 (μg/L)	338.6 ± 113.6	310.4 ± 74.6	338.4 ± 94.1
ELF >9.8	9 (45)	12 (57)	5 (24)

Shown are mean ± SD or n (%). C4, 7alpha-hydroxy-4-cholesten-3-one; ELF, Enhanced Liver Fibrosis; ERCP, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance cholangiopancreatography; PIIINP, N-terminal propeptide of type III collagen; Pro-C3, neoepitope-specific N-terminal propeptide of type III collagen; SD, standard deviation; TIMP-1, tissue inhibitor of metalloproteinase 1; UDCA, ursodeoxycholic acid

PRO-C3 – threshold 14.9 and 26.0





Tertile	n	Median	Min	Max
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[14.8,38.9)	46	24.8	14.9	38.8
[38.9,374]	46	67.1	39.3	374.4

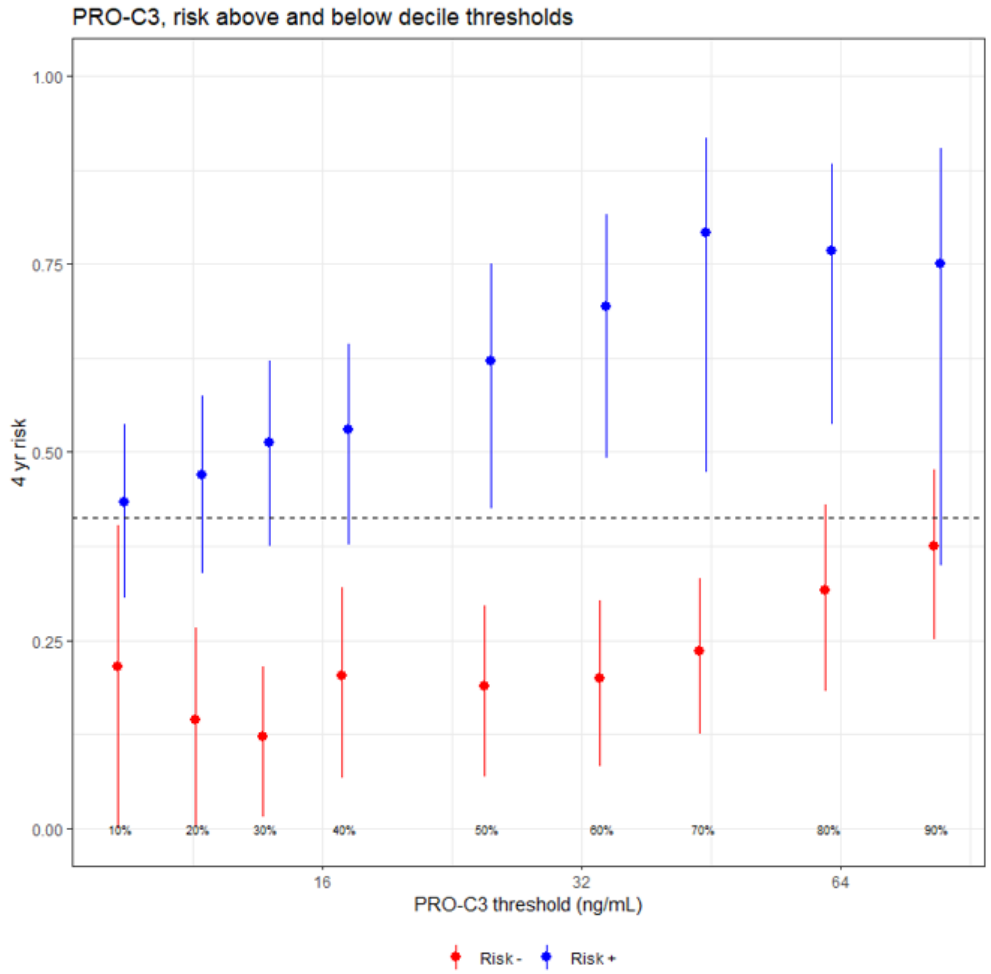
Group	n	Median	Min	Max	Risk [95% CI]
[5.86,14.9)	46	10.8	5.9	14.6	0.14 [0.03, 0.24]
[14.9,374]	92	39.0	14.9	374.4	0.52 [0.38, 0.63]

Min value 2nd tertile

Group	n	Median	Min	Max	Risk [95% CI]
[5.86,26)	71	12.7	5.9	25.9	0.19 [0.07, 0.29]
[26,374]	67	55.9	26.4	374.4	0.63 [0.44, 0.76]

Cut off from aldafermin study

PRO-C3 risk deciles



	Decile (ng/mL)	Group	Risk [95% CI]	Hazard ratio [95% CI]
10%	9.3	Above	0.43 [0.31, 0.54]	1.82 [0.56, 5.85]
10%	9.3	Below	0.21 [0.00, 0.40]	
20%	11.5	Above	0.47 [0.34, 0.58]	3.06 [1.10, 8.52]
20%	11.5	Below	0.14 [0.00, 0.27]	
30%	13.7	Above	0.51 [0.37, 0.62]	4.05 [1.60, 10.24]
30%	13.7	Below	0.12 [0.02, 0.22]	
40%	17.0	Above	0.53 [0.38, 0.64]	3.19 [1.54, 6.60]
40%	17.0	Below	0.20 [0.07, 0.32]	
50%	24.8	Above	0.62 [0.42, 0.75]	4.62 [2.29, 9.30]
50%	24.8	Below	0.19 [0.07, 0.30]	
60%	33.9	Above	0.69 [0.49, 0.82]	5.84 [3.03, 11.26]
60%	33.9	Below	0.20 [0.08, 0.30]	
70%	44.3	Above	0.79 [0.47, 0.92]	4.98 [2.76, 9.00]
70%	44.3	Below	0.24 [0.13, 0.33]	
80%	61.9	Above	0.77 [0.54, 0.88]	4.60 [2.57, 8.22]
80%	61.9	Below	0.32 [0.18, 0.43]	
90%	82.7	Above	0.75 [0.35, 0.90]	3.33 [1.64, 6.75]
90%	82.7	Below	0.37 [0.25, 0.48]	

PRO-C6 and Outcome

NEJM Evidence

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ORIGINAL ARTICLE

Endotrophin, a Collagen VI Formation–Derived Peptide, in Heart Failure

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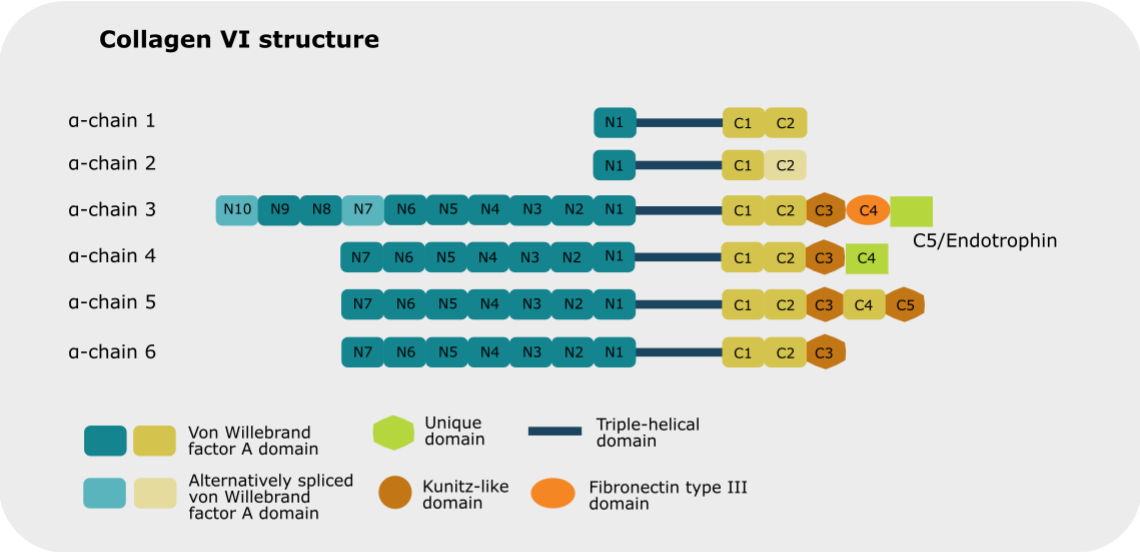
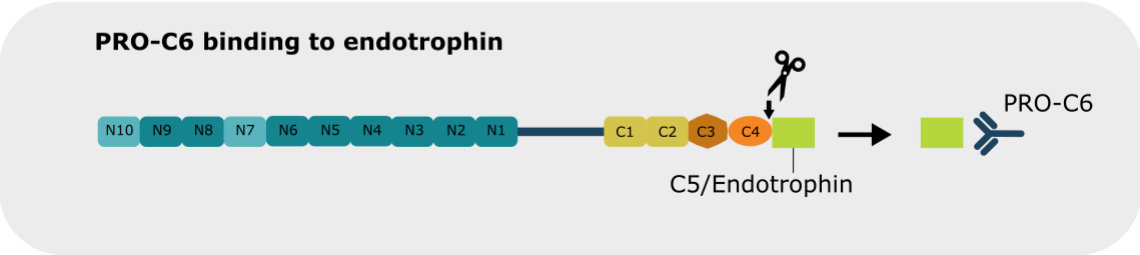
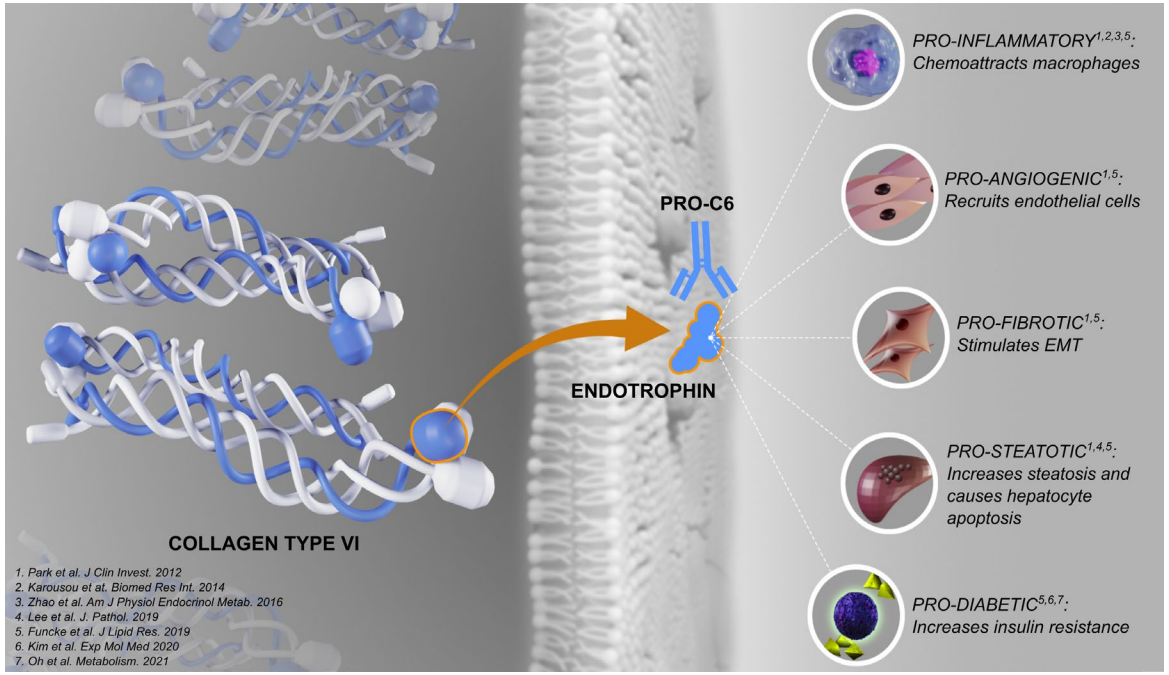
PRO-C6 and endotrophin



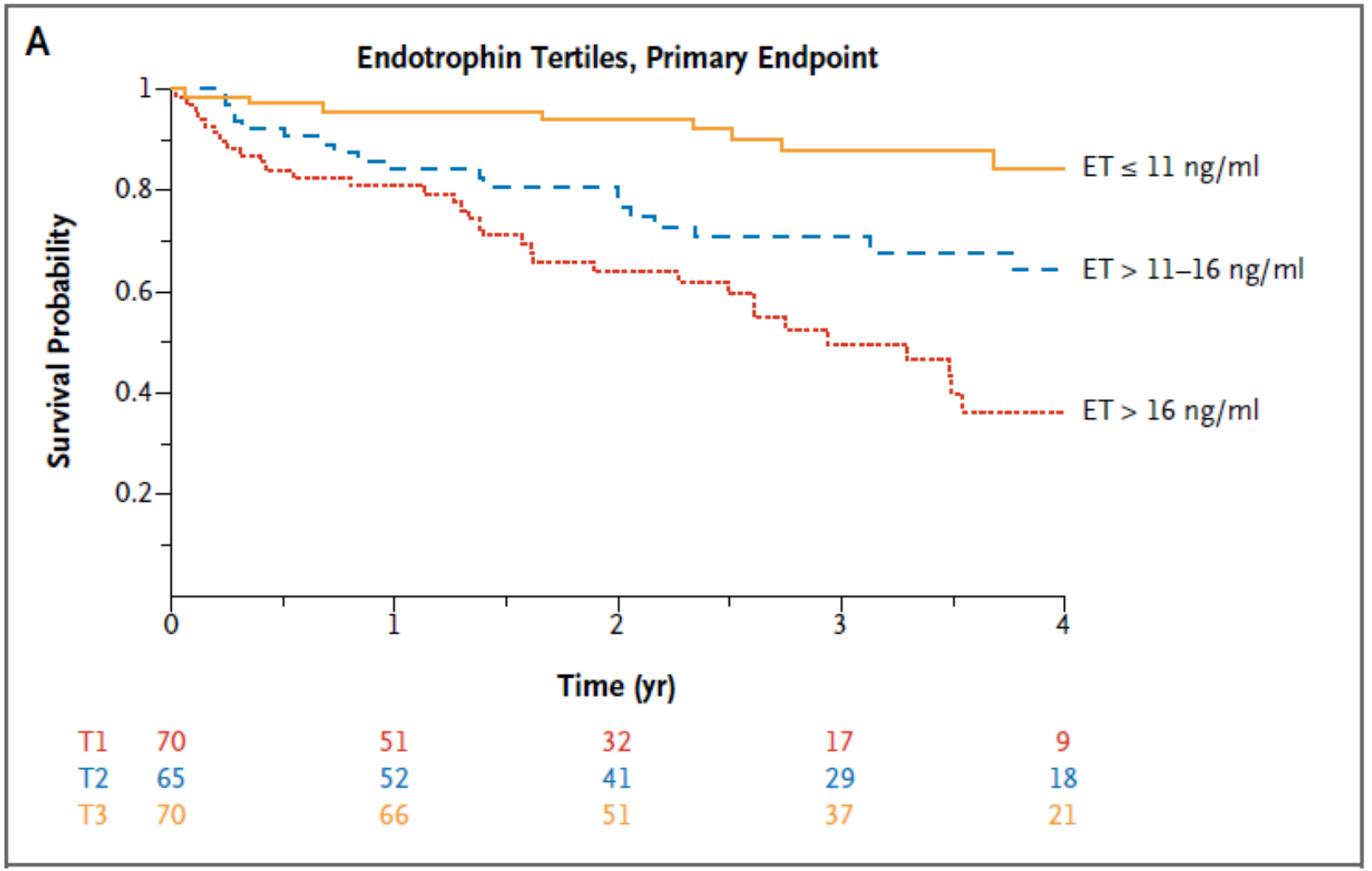




Genovese F., Bager C. et al. Manuscript in preparation

Kremer D. et al Nephrol Dial Transplant. 2023

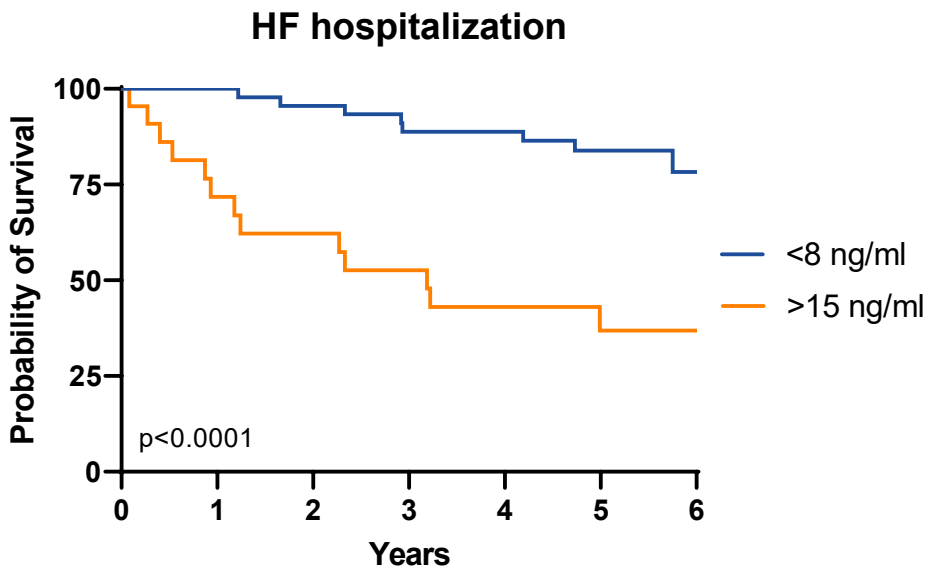
Endotrophin is prognostic for adverse outcome in HFpEF – the bad collagens kills!



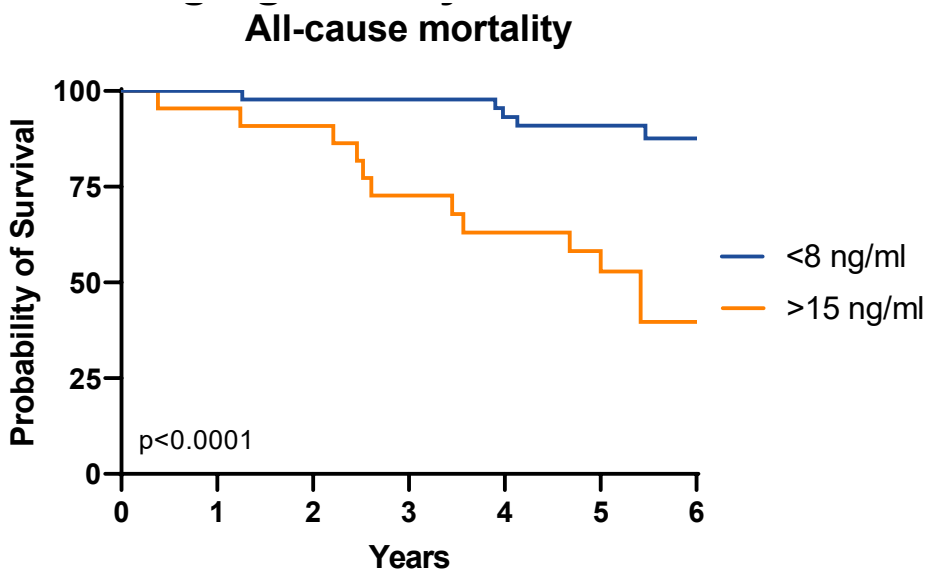
TOPCAT biomarker substudy (n=205). Primary endpoint: composite of cardiovascular mortality, aborted cardiac arrest, or hospitalization for the management of HF

Understanding fibroblast activity is crucial for risk estimation

Type VI collagen formation increases risk of adverse outcomes by a factor of 10!



HR = 9.4



HR = 10.1

For heart failure patients, an increase of 1 ng/ml in PRO-C6 levels leads to a 12.5% increased risk of CV mortality

In the general population, an increase of 1 ng/ml in PRO-C6 levels leads to a 9.2% increased risk of all-cause mortality

PRO-C6: Formation of collagen type VI and endotrophin

NORDIC BIOSCIENCE

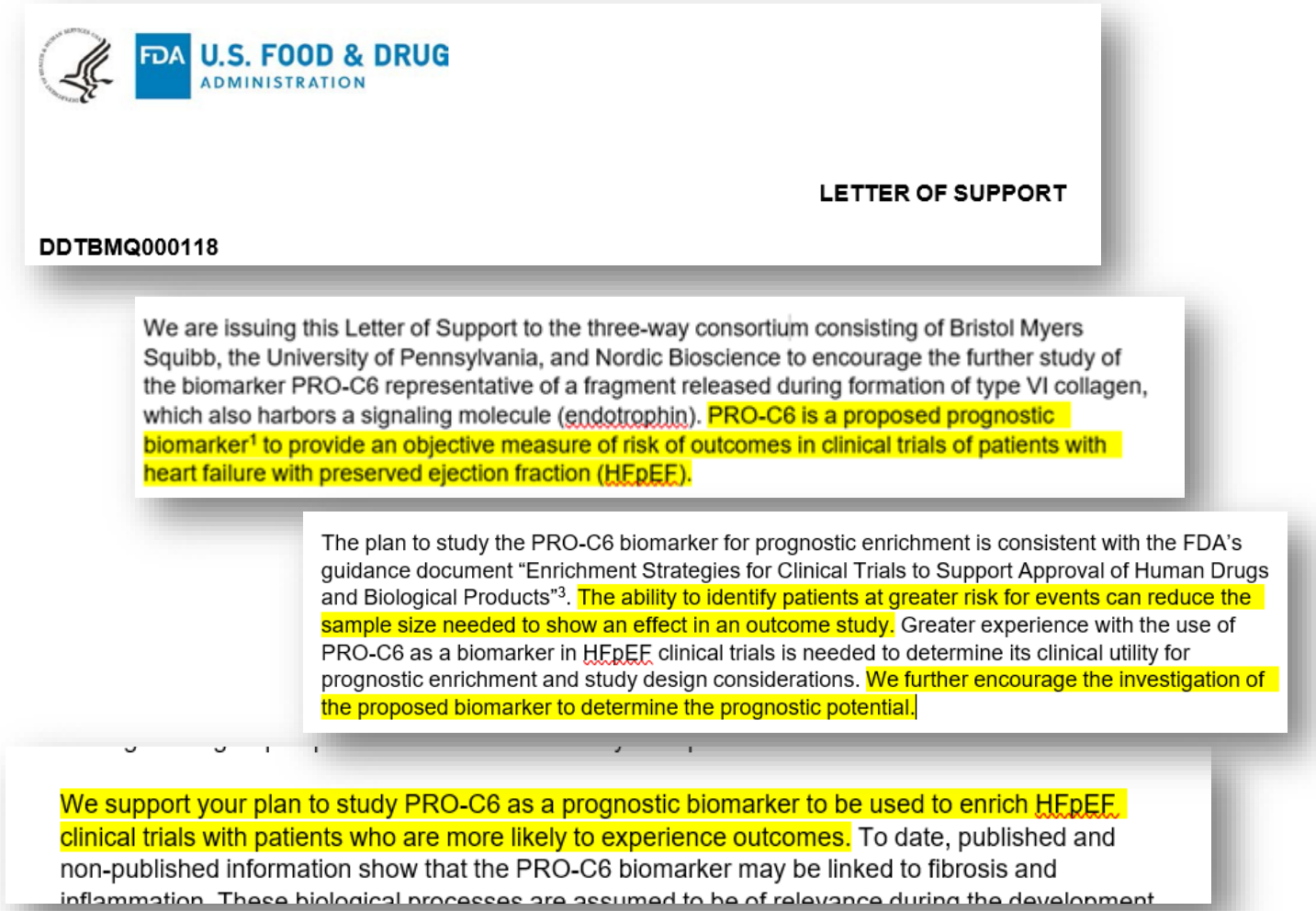
LoS Language Demonstrates the Potential Value FDA Sees in PRO-C6 as a Biomarker in HFpEF

What is a Letter of Support (LoS)?

- Briefly describes CDER's thoughts on the potential value of a biomarker and encourages further evaluation.
- An LoS is issued for promising biomarkers which have not yet been accepted into the CDER BQP

Why Issue a Letter of Support?

- The intent of the LOS is to **enhance the visibility of these biomarkers**, make public **FDA's support** for continued development, and encourage data sharing and collaboration.



U.S. FOOD & DRUG ADMINISTRATION

LETTER OF SUPPORT

DDTBMQ000118

We are issuing this Letter of Support to the three-way consortium consisting of Bristol Myers Squibb, the University of Pennsylvania, and Nordic Bioscience to encourage the further study of the biomarker PRO-C6 representative of a fragment released during formation of type VI collagen, which also harbors a signaling molecule (endotrophin). PRO-C6 is a proposed prognostic biomarker[1] to provide an objective measure of risk of outcomes in clinical trials of patients with heart failure with preserved ejection fraction (HFpEF).

The plan to study the PRO-C6 biomarker for prognostic enrichment is consistent with the FDA's guidance document "Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products"[3]. The ability to identify patients at greater risk for events can reduce the sample size needed to show an effect in an outcome study. Greater experience with the use of PRO-C6 as a biomarker in HFpEF clinical trials is needed to determine its clinical utility for prognostic enrichment and study design considerations. We further encourage the investigation of the proposed biomarker to determine the prognostic potential.

We support your plan to study PRO-C6 as a prognostic biomarker to be used to enrich HFpEF clinical trials with patients who are more likely to experience outcomes. To date, published and non-published information show that the PRO-C6 biomarker may be linked to fibrosis and inflammation. These biological processes are assumed to be of relevance during the development

HFpEF: Heart failure with preserved ejection fraction

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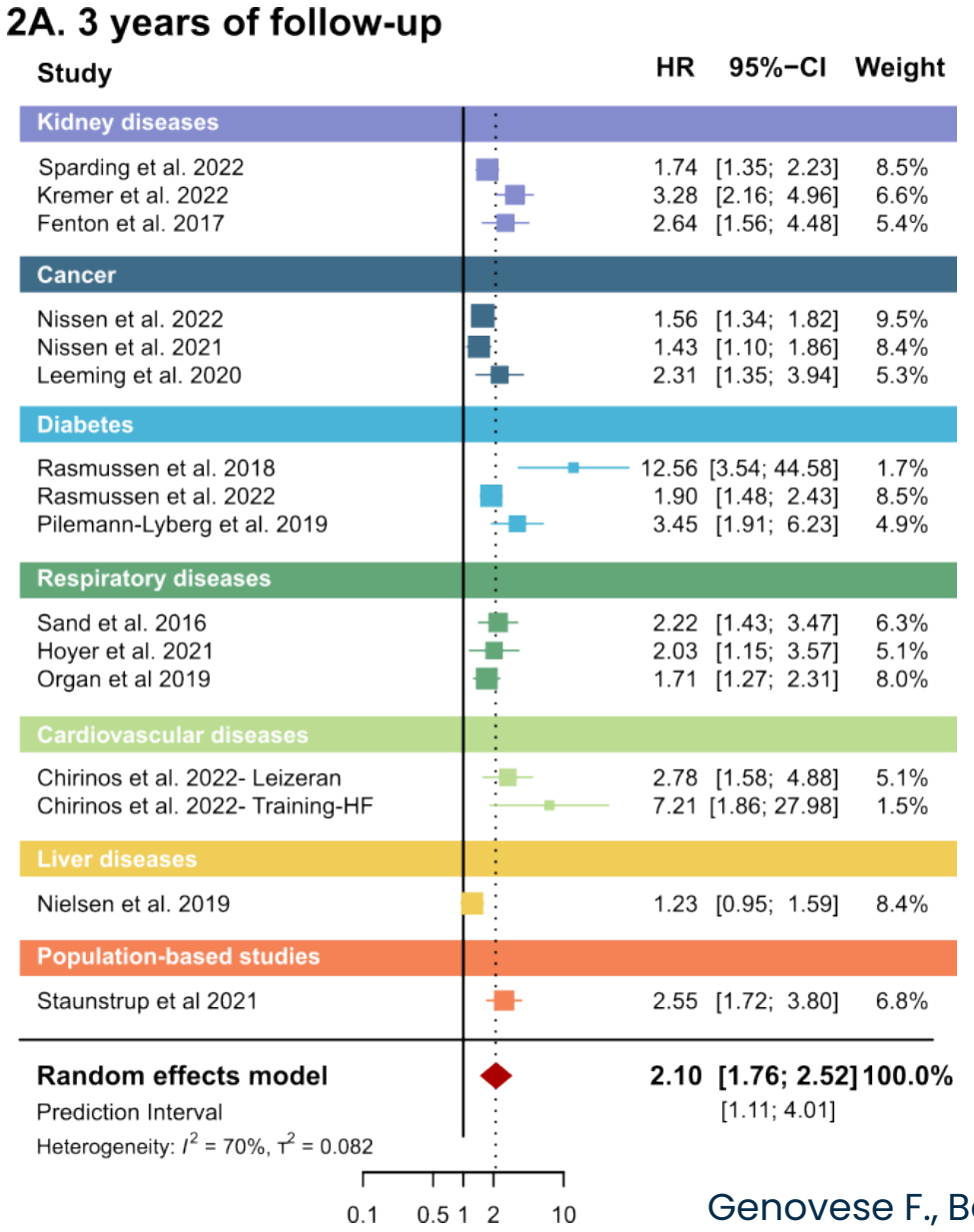
Fibroblast activity kills



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Fibroblast Activities Kills – please modulate them