Clonal hematopoesis of Indeterminate Potential (CHIP) increases mortality risk in Coronary Artery Disease

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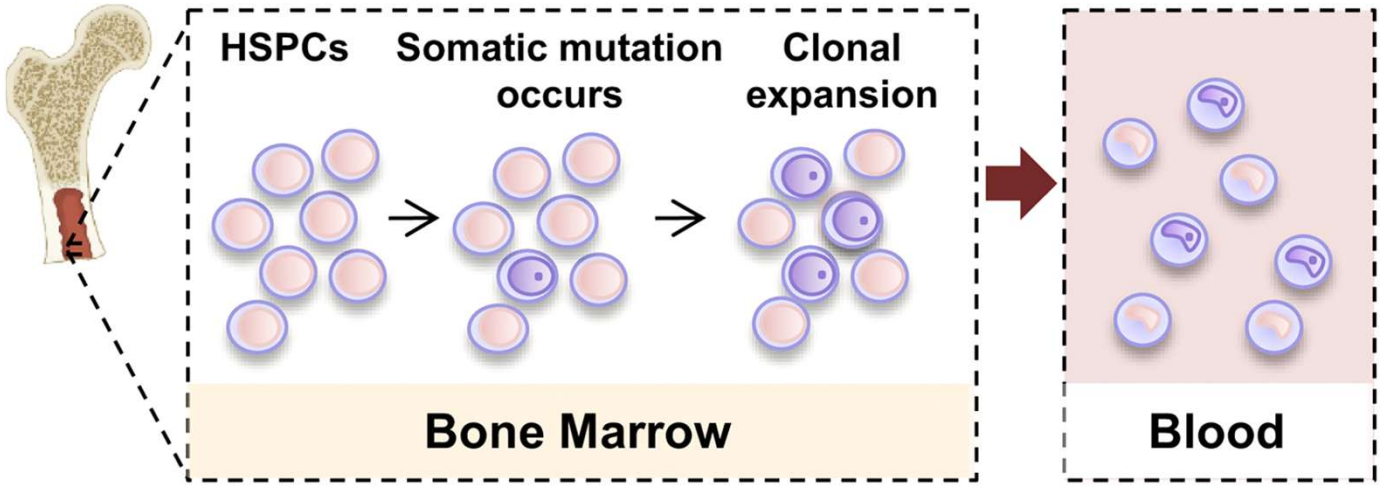
06.11.2024 – DigiMed Bayern Symposium

Deutsches Herzzentrum München
des Freistaates Bayern
Klinik a. d. Technischen Universität München

RELEVANCE OF CHIP

Definition



Presence of acquired mutation, VAF ≥2%, no hematological neoplasms

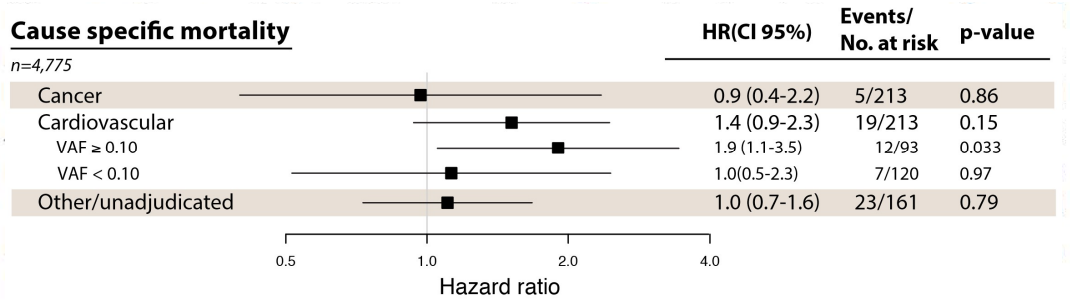
Blood 2015: Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes; Jul 2;126(1):9-16.
Atherosclerosis 2020: Clonal hematopoiesis driven by somatic mutations: A new player inatherosclerotic cardiovascular disease; 297 (2020), 120-126

Clinical relevance – CHIP

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Age-Related Clonal Hematopoiesis Associated with Adverse Outcomes



CONCLUSIONS

Age-related clonal hematopoiesis is a common condition that is associated with increases in the risk of hematologic cancer and in all-cause mortality, with the latter possibly due to an increased risk of cardiovascular disease. (Funded by the National Institutes of Health and others.)

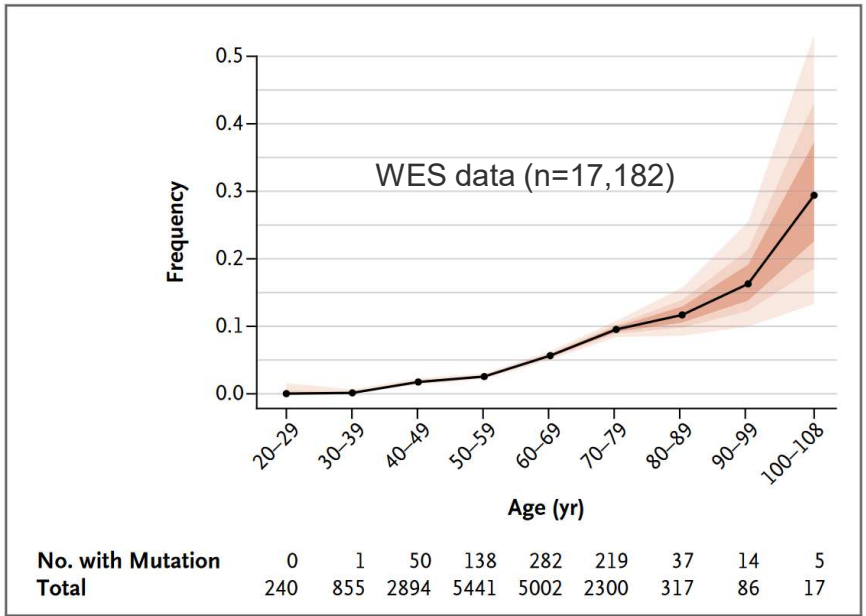


Figure 1. Prevalence of Somatic Mutations, According to Age.
Colored bands, in increasingly lighter shades, represent the 50th, 75th, and 95th percentiles.

NEJM 2014: Age-related clonal hematopoiesis associated with adverse outcomes; 371(26):2488-98

Clinical relevance – CHIP

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Risks associated with developing **incident coronary heart disease** using traditional CV risk factors and mutations (Jackson Heart Study and Fusion)

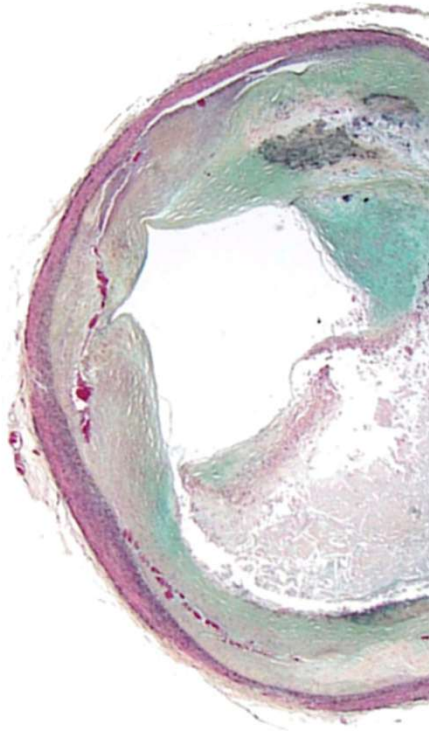
RF (n=2,286)	HR (95%CI)	P-value
CHIP (VAF ≥ 0.1)	**4.4 (1.9-10.5)**	**<0.001**
T2D	3.5 (2.2-5.5)	<0.001
TC > 240mg/dl	2.0 (1.3-3.1)	<0.001
Smoking (ever)	1.6 (1.1-2.5)	0.02
Hypertension	1.4 (0.9-2.3)	0.15
BMI > 25	1.3 (0.6-2.8)	0.42

NEJM 2014: Age-related clonal hematopoiesis associated with adverse outcomes; 371(26):2488-98

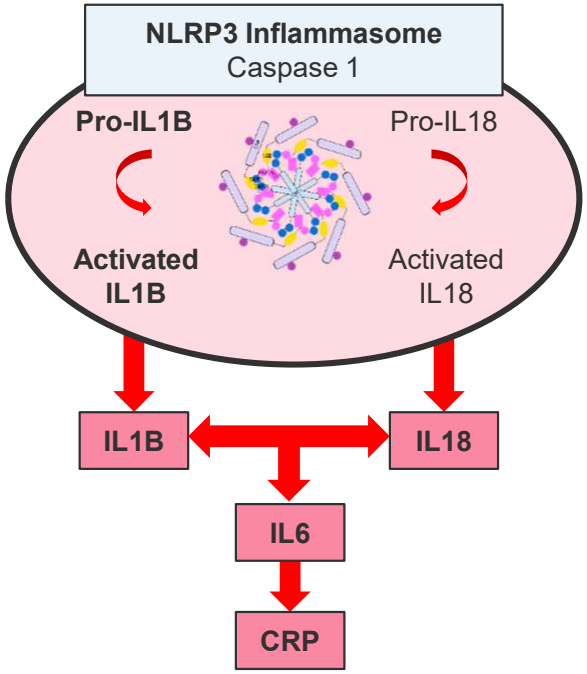
HYPOTHESIS

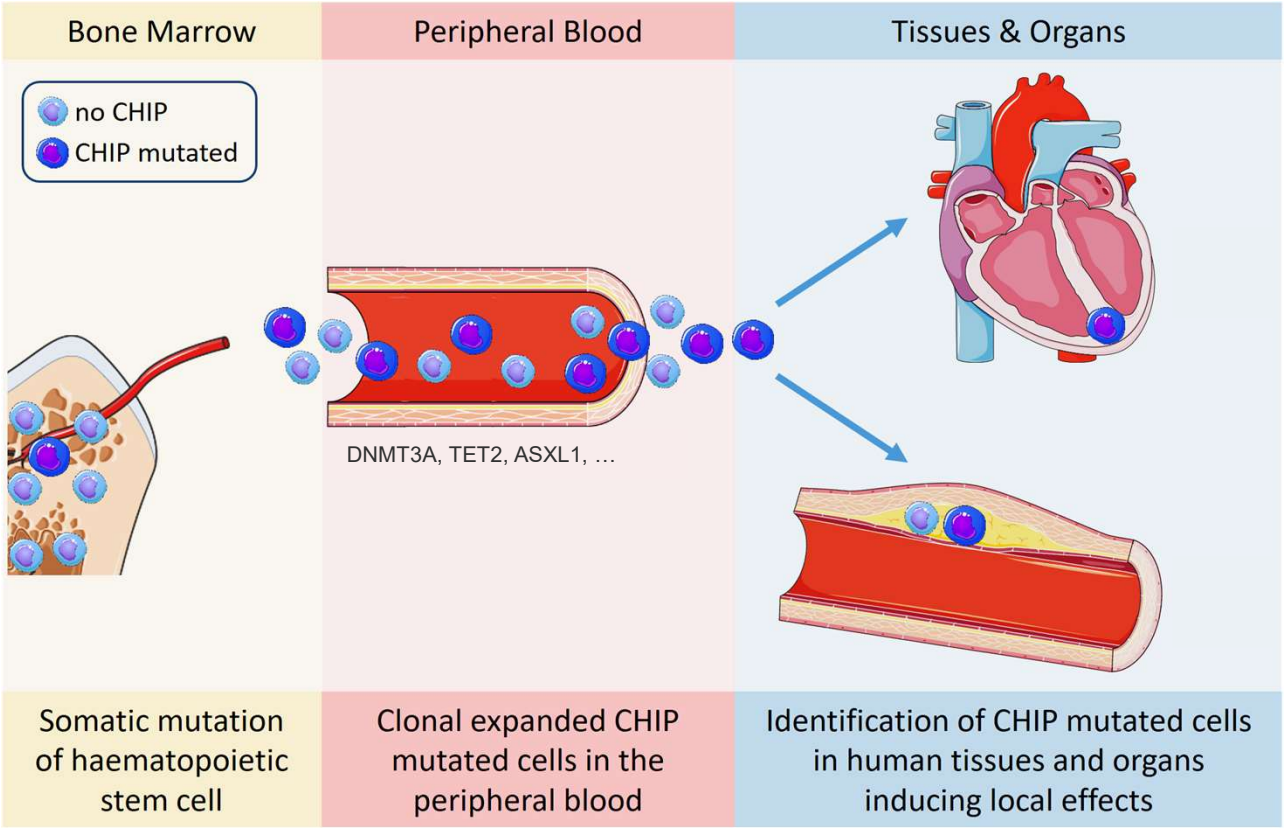
Hypothesis

- **CAD CHIP** mutation carriers are **at increased mortality risk**
- **increased risk** of cardiovascular events (MI, stroke, death) is **based on a more complex atherosclerotic phenotype**
- **underlying mechanisms** (i.e. inflammatory signatures) might be identified studying **CHIP affected macrophages**



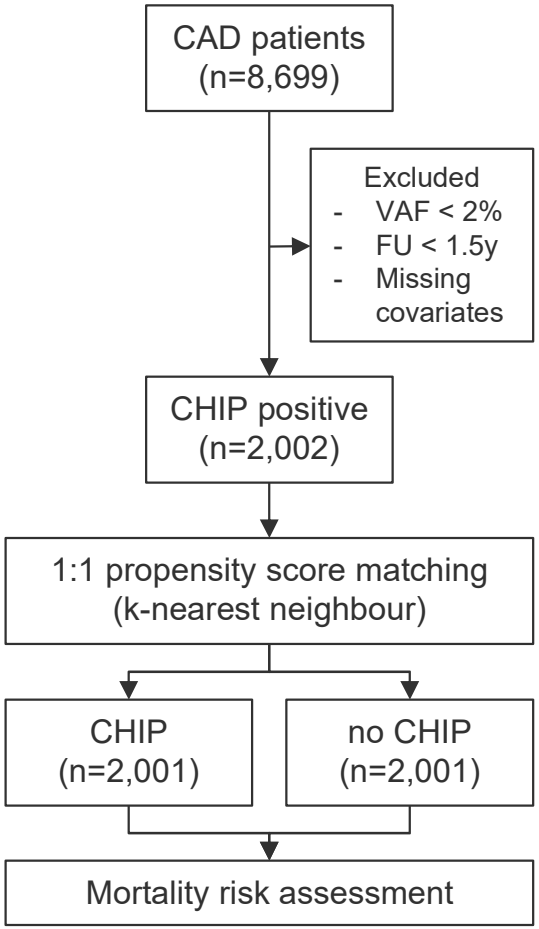
CHIP in atherosclerotic plaques





HUMAN CLINICAL DATA

CHIP CAD cohort – Study workflow



von Scheidt et al. - unpublished

CHIP CAD cohort – baseline characteristics

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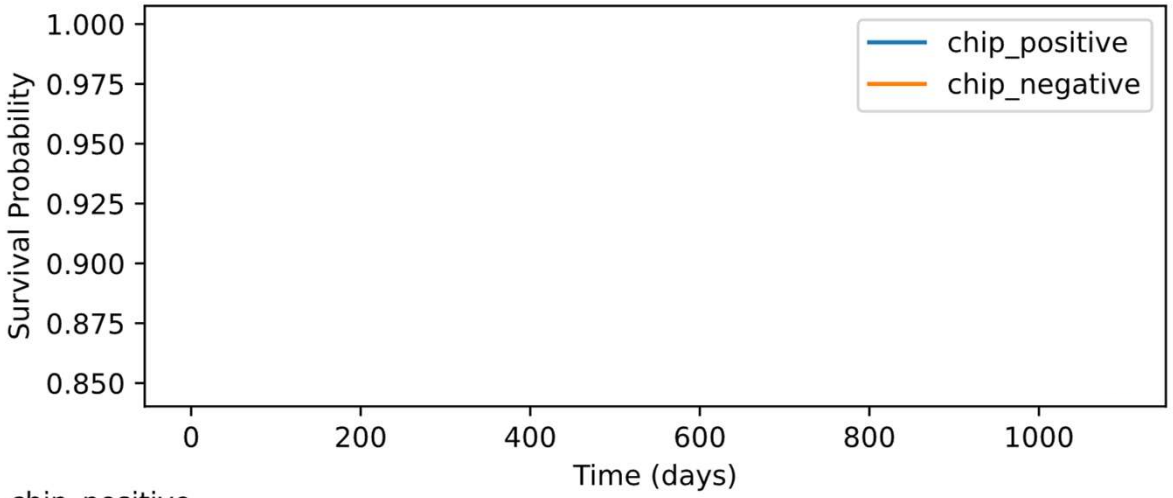
	Unmatched cohort			
	CHIP (n=2002)	no CHIP (n=5931)	Standardized difference	CI of SD
Age	74.1 ± 9.2	69.0 ± 10.9	**0.511**	[0.460, 0.566]
Sex (f)	494 (24.7%)	1364 (23.0%)	**0.032**	[-0.019, 0.083]
BMI	27.4 ± 4.3	27.6 ± 4.7	**-0.064**	[-0.115, -0.013]
Height	1.72 ± 0.1	1.73 ± 0.1	**-0.122**	[-0.173, -0.071]
Weight	81.4 ± 15.3	83.2 ± 16.2	**-0.119**	[-0.169, -0.068]
Hypertension	1829 (91.4%)	5233 (88.2%)	**0.086**	[0.036, 0.137]
Nicotine ever	769 (38.4%)	2510 (42.3%)	**-0.065**	[-0.116, -0.015]
Diabetes	585 (29.2%)	1551 (26.2%)	**0.056**	[0.005, 0.106]
Insulin	160 (8.0%)	465 (7.8%)	**0.005**	[-0.046, 0.055]
Family history	541 (27.0%)	1857 (31.3%)	**-0.078**	[-0.128, -0.027]
LV function	1271 (63.5%) 658 (32.9%) 73 (3.7%)	3804 (64.1%) 1938 (32.7%) 189 (3.2%)	**0.003**	[-0.047, 0.054]
Prior MI	537 (26.8%)	1814 (30.6%)	**-0.068**	[-0.119, -0.018]

von Scheidt et al. - unpublished

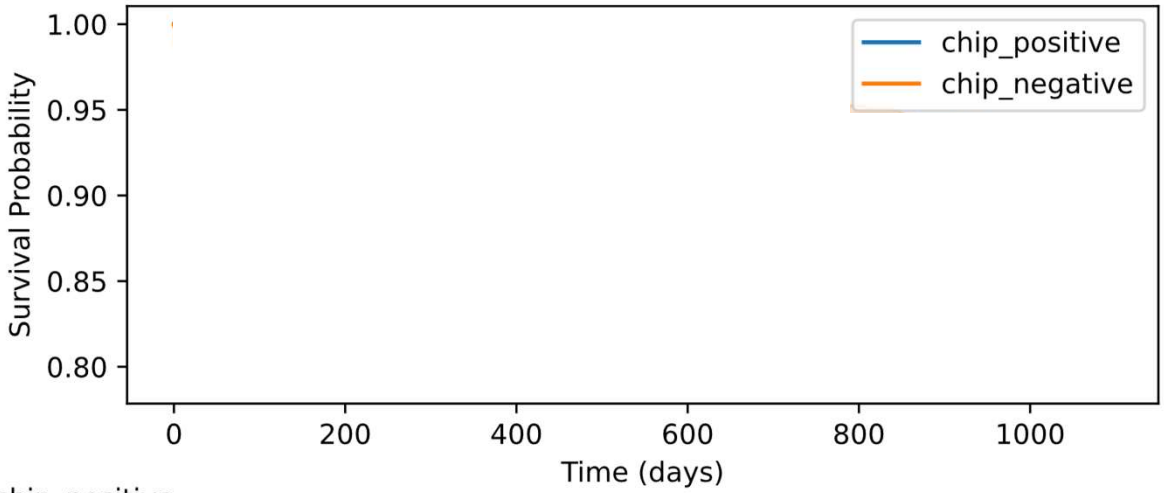
CHIP in CAD – Mortality (VAF>2%)



chip_positive						
At risk	2001	1944	1894	1845	1800	1722
Censored	0	0	0	0	0	28
Events	0	57	107	156	201	251
chip_negative						
At risk	2001	1954	1930	1895	1831	1778
Censored	0	0	0	13	41	58
Events	0	47	71	93	129	165

von Scheidt et al. - unpublished

CHIP in CAD – Mortality (VAF>10%)



chip_positive						
At risk	592	571	548	531	511	486
Censored	0	0	0	0	0	7
Events	0	21	44	61	81	99
chip_negative						
At risk	592	577	571	561	539	523
Censored	0	0	0	4	15	21
Events	0	15	21	27	38	48

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CHIP in CAD – Individual CHIP Genes

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VAF ≥2%

Affected gene	# of CHIP mutations	HR (death)
DNMT3A	**994**	**1.35**
TET2	**597**	**1.36**
ASXL1	**243**	**1.74**
PPM1D	**156**	**1.95**
TP53	107	1.66
SF3B1	**87**	**1.82**
SRSF2	**73**	**2.32**
JAK2	64	1.76
CBL	46	1.17
ZRSR2	40	1.49
U2AF1	**40**	**2.55**
MPL	17	2.15
CALR	9	2.70

VAF ≥10%

JAK2	**29**	**3.78**
CALR	**5**	**11.5**

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MISSION BIOBANK DATA

MISSION Biobank (n=1,517)

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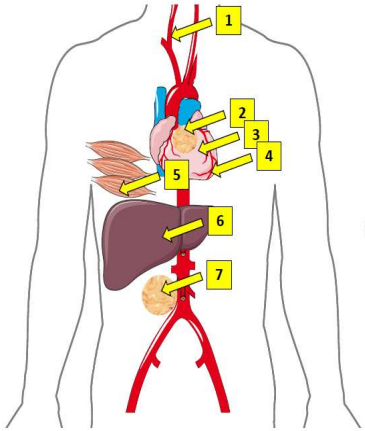
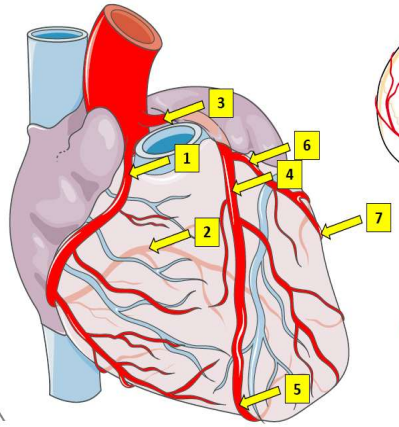
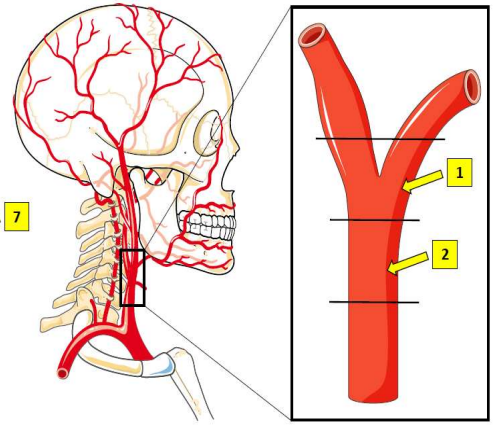
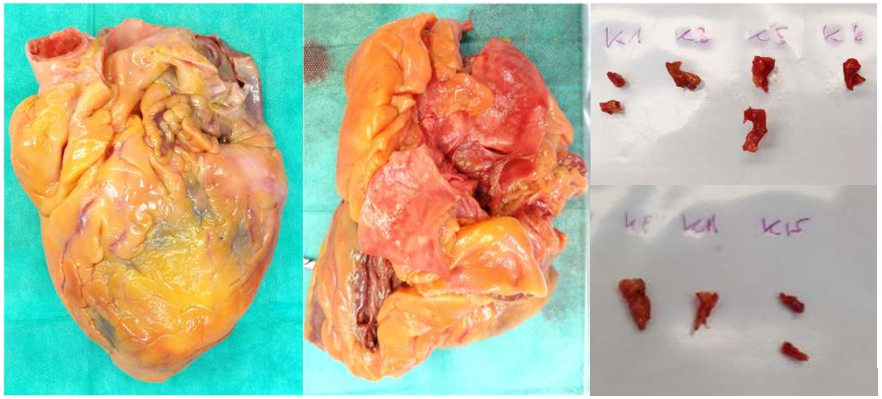
MISSION Biobank CHIP (n=359)

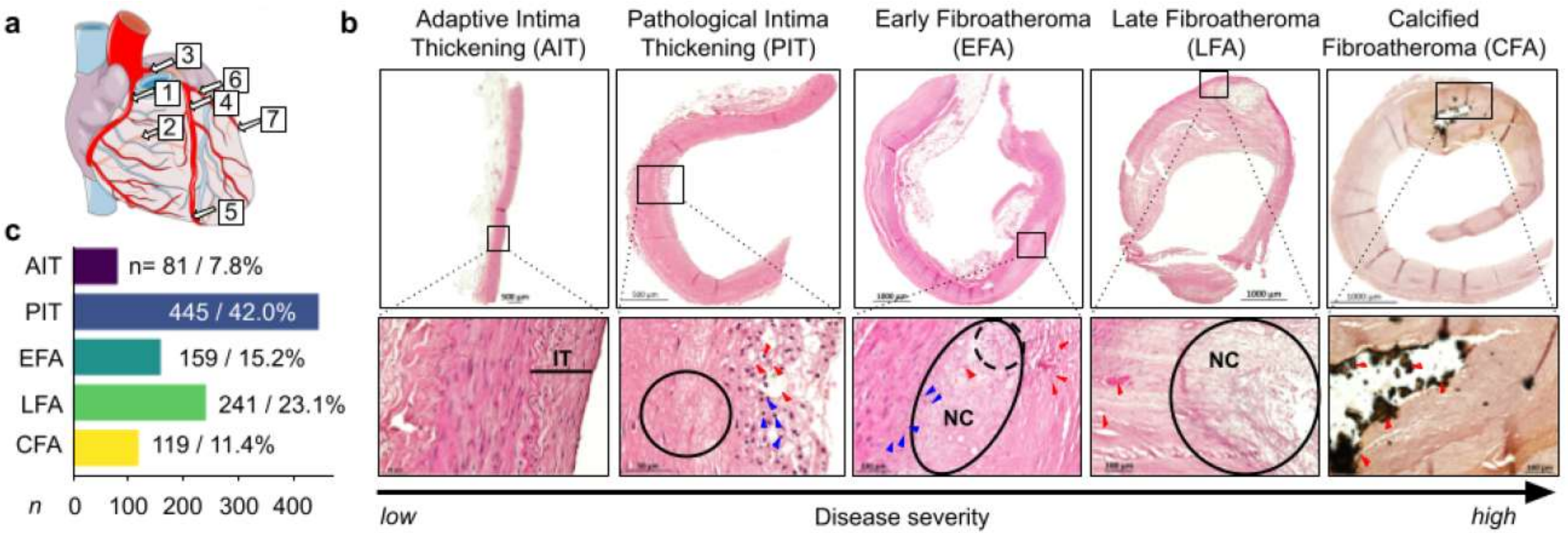






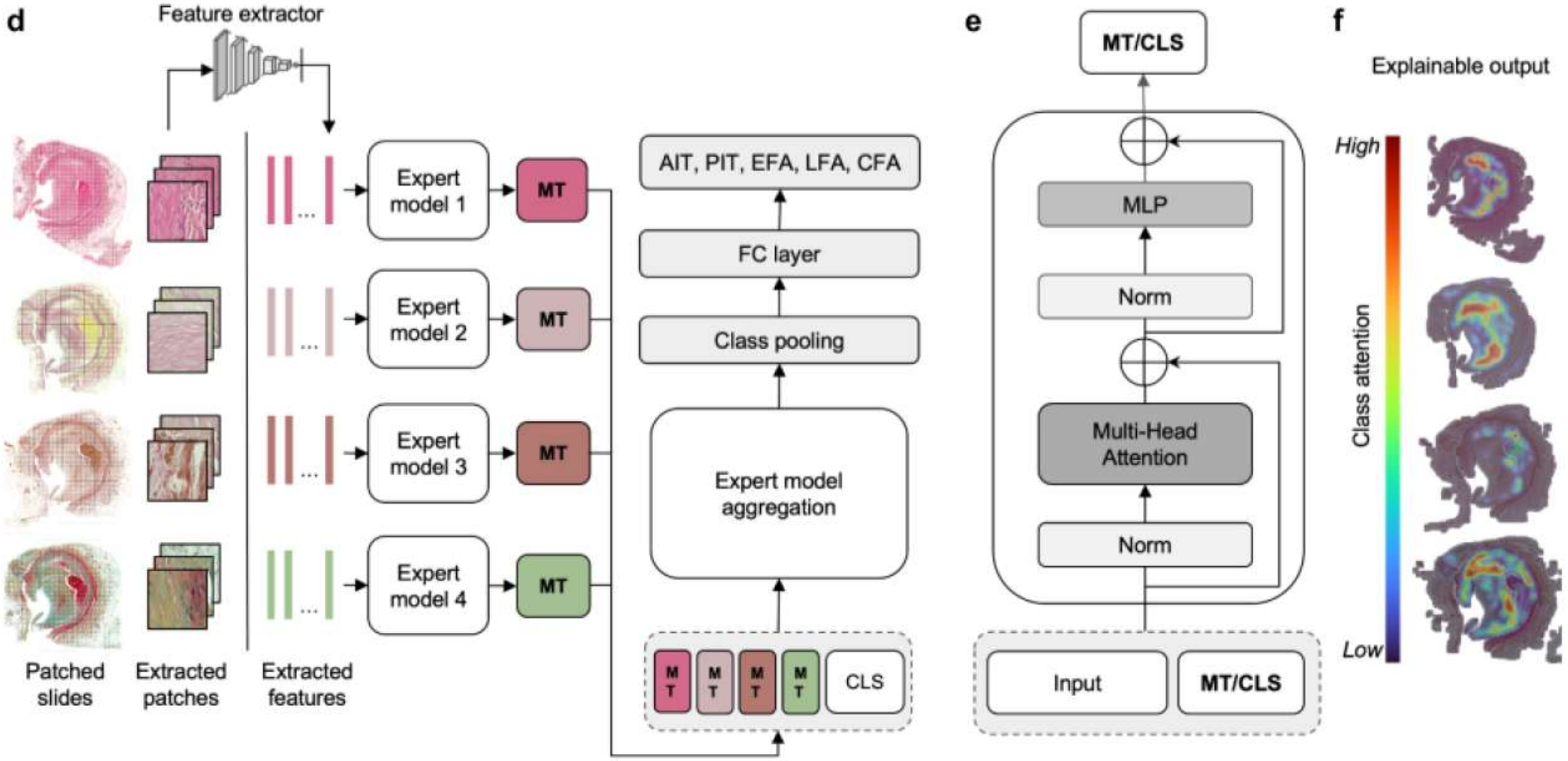


UNICORN – Multi Modal Transformer



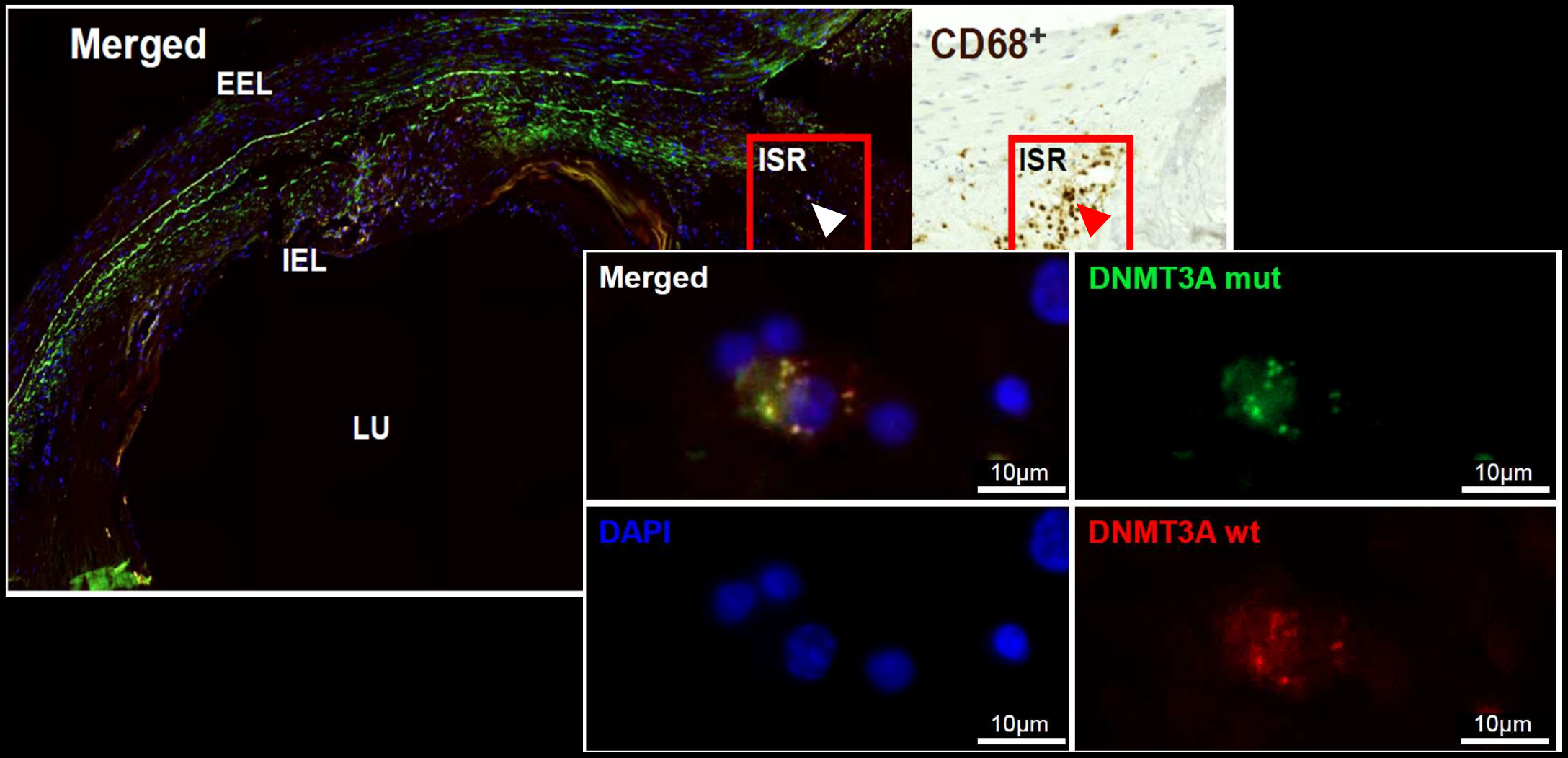
Koch et al. - unpublished

UNICORN – Multi Modal Transformer



Koch et al. - unpublished

MutaFISH – DNMT3A, c.2333T>G (RNA based)



von Scheidt et al. - Leukocytes carrying Clonal Hematopoiesis of Indeterminate Potential (CHIP) Mutations invade Human Atherosclerotic Plaque. medRxiv 2023

TET2 CHIP in MISSION Biobank – Cohort

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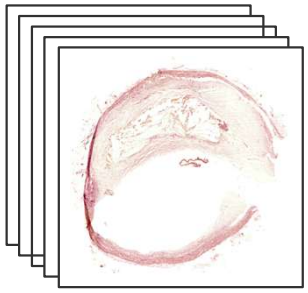
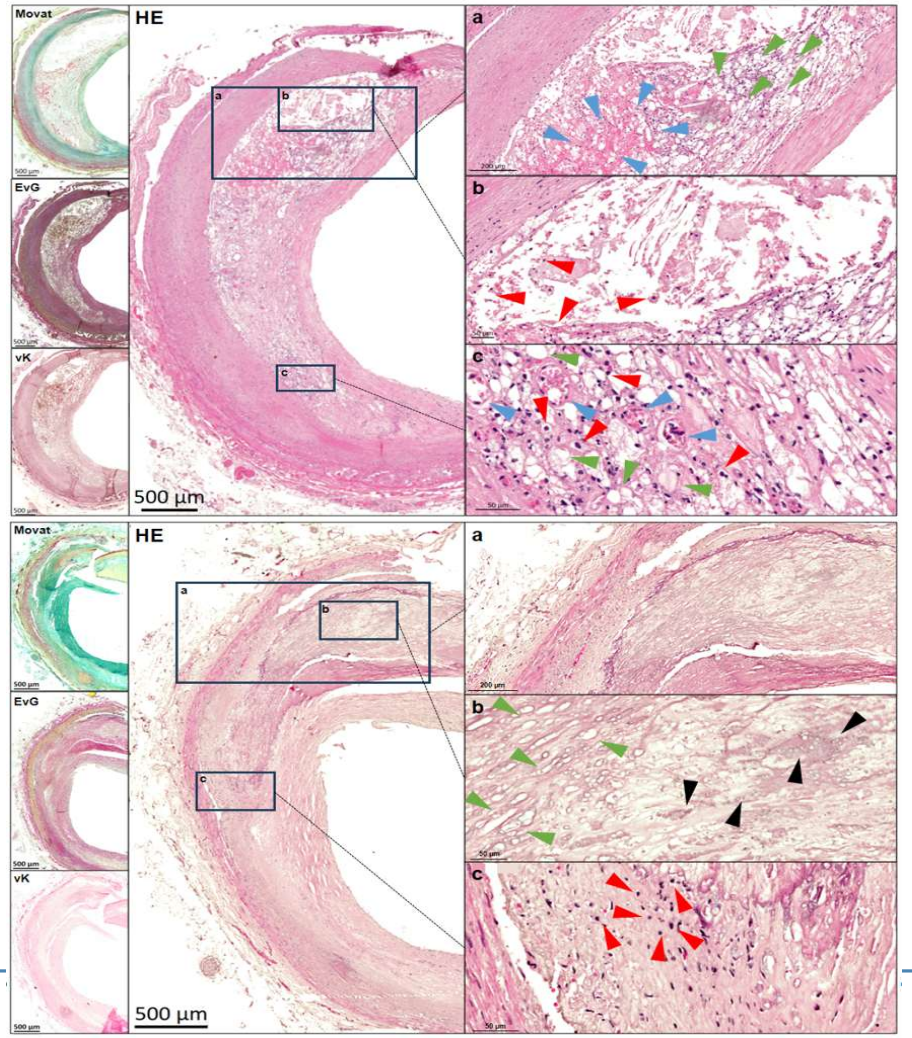
	TET2 CHIP (n=26)	no CHIP (n=13)	p-value
Age	79.9 ± 6.3	79.4 ± 7.6	**0.83**
Sex (f)	9 (34.6%)	4 (30.8%)	**0.81**
BMI	26.3 ± 4.3	26.3 ± 2.9	**1.00**
Height	1.67 ± 0.1	1.68 ± 0.1	**0.77**
Weight	74.1 ± 15.4	74.1 ± 8.1	**1.00**
PMI	39.6 ± 15.8	42.2 ± 17.5	**0.64**



More complex CAD in TET2 CHIP
based on histological assessment.

CHIP

no CHIP



Age and sex matched (n=26 TET2-CHIP vs. n=13 non-CHIP)

TET2 CHIP in MISSION Biobank – Cohort

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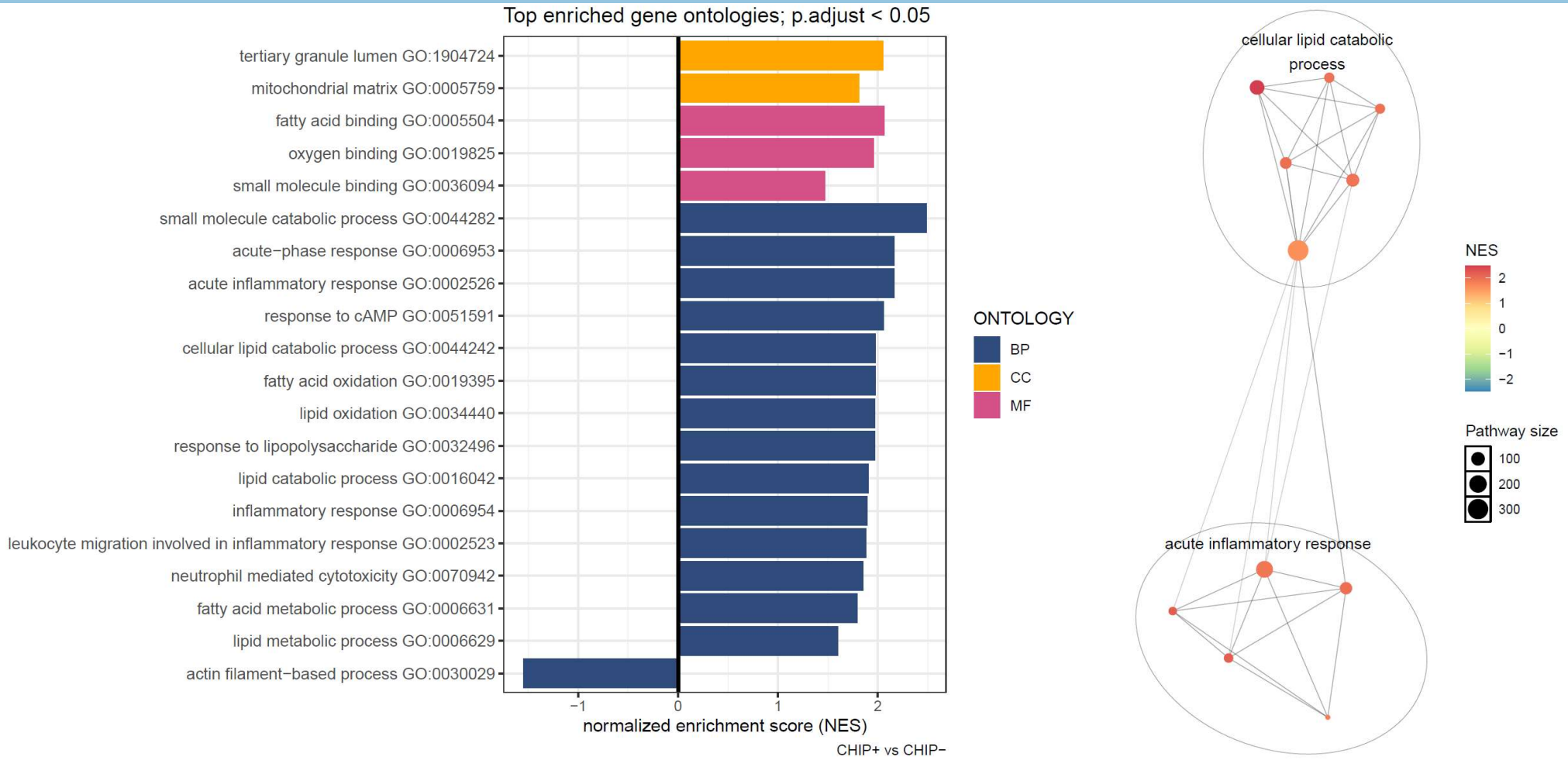
More complex CAD in TET2 CHIP based on histological assessment.

AG Prof. Mann

Age and sex matched (n=26 TET2-CHIP vs. n=13 non-CHIP)

TET2 CHIP in MISSION Biobank – Proteomics



Age and sex matched (n=26 TET2-CHIP vs. n=13 non-CHIP)

TET2 CHIP in MISSION Biobank – Proteomics

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PLAQUE STABILITY

Age and sex matched (n=26 TET2-CHIP vs. n=13 non-CHIP)

TET2 CHIP in MISSION Biobank – Proteomics

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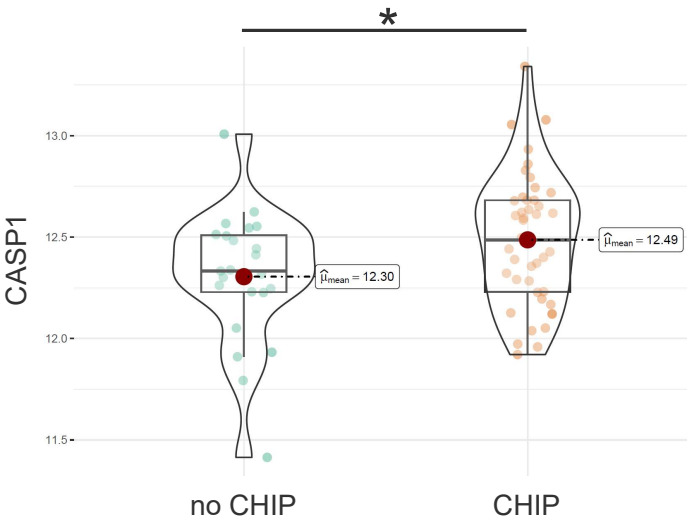
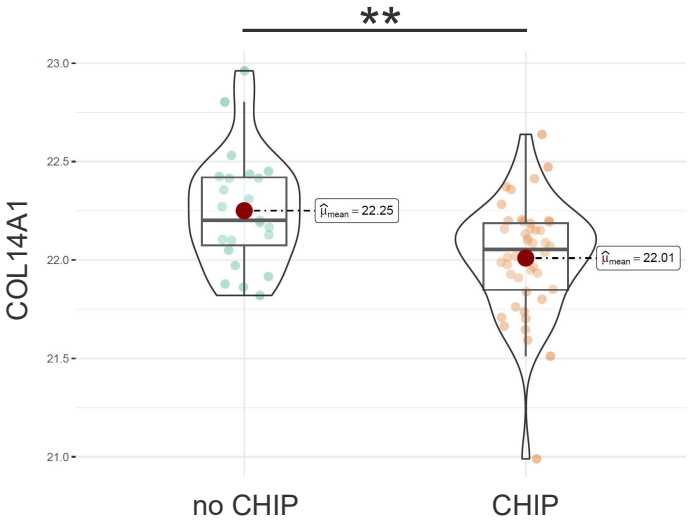
Caspase-1



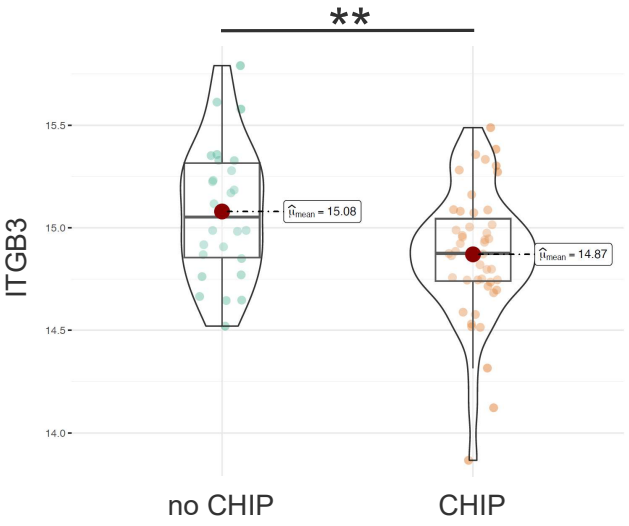
High Caspase-1 levels are associated with increased NLRP3-inflammasome activity and IL1b production.

Collagen-14A1



High COL14A1 levels are associated with plaque stability.

Integrin-Beta3



High ITGB3 levels are associated with atheroprotection and reduced inflammation.

Conclusion: TET2 CHIP status is associated with atherosclerotic plaque instability.

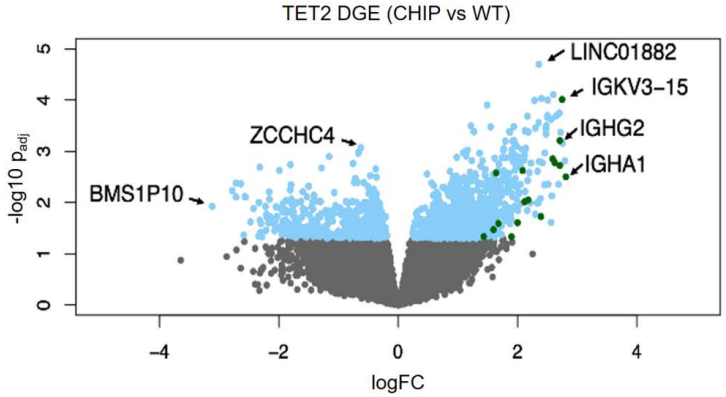
Age and sex matched (n=26 TET2-CHIP vs. n=13 non-CHIP)

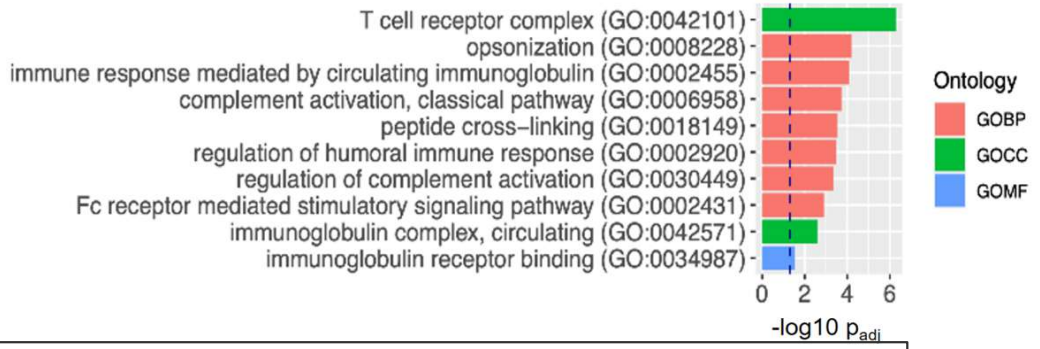
STARNET MACROPHAGE DATA

RNAseq data – TET2 CHIP macrophages

	TET2 CHIP (n=3)	no CHIP (=21)	p-value
Age	60.3 ± 12.0	61.8 ± 8.2	0.82
Sex (m)	3 (100%)	21 (100%)	1
BMI	28.0 ± 4.9	28.6 ± 5.0	0.86
Hypertension	2	14 (n=20)	1
Dyslipidemia	2	14 (n=20)	1
Nicotine ever	2	7 (n=20)	0.54
Diabetes	0	4 (n=20)	1
Prior MI	1	7 (n=20)	1

Traits x TET2 CHIP status	p-value
Atherosclerotic lesions	1.35×10^{-40}
Complexity of CAD (SYNTAX score)	1.23×10^{-11}
Coronary artery Disease	2.55×10^{-10}
BMI	<0.001
Creatinine plasma levels	0.002
Total cholesterol	0.02





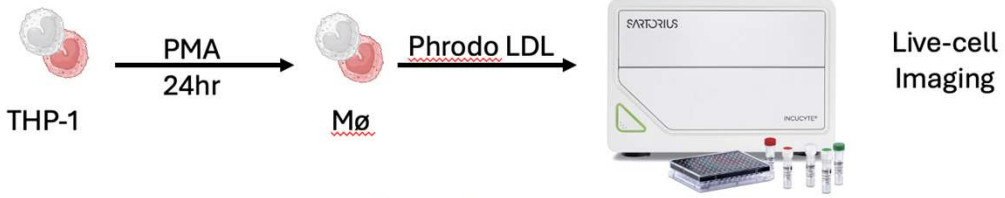
Conclusion: TET2 CHIP status in human monocyte derived macrophages is associated with atherosclerosis, CAD complexity and upregulation of inflammatory pathways.

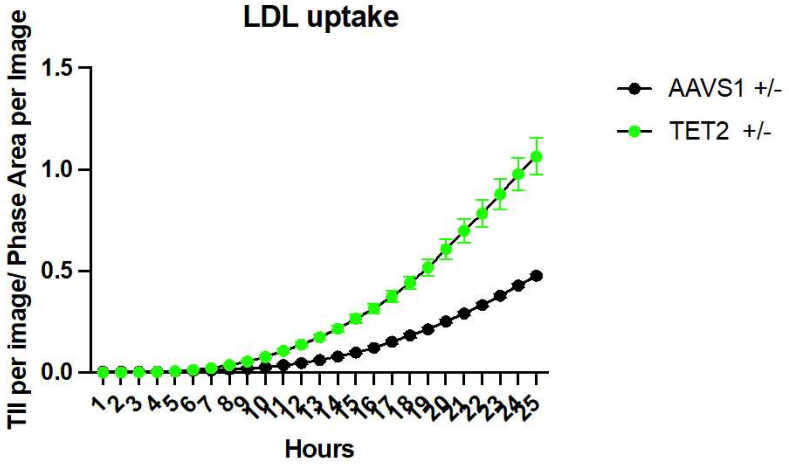
STARNET – Collaboration with Prof. Björkegren

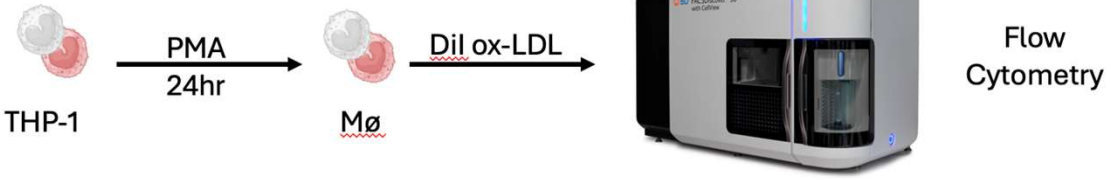
IN-VITRO MACROPHAGE DATA

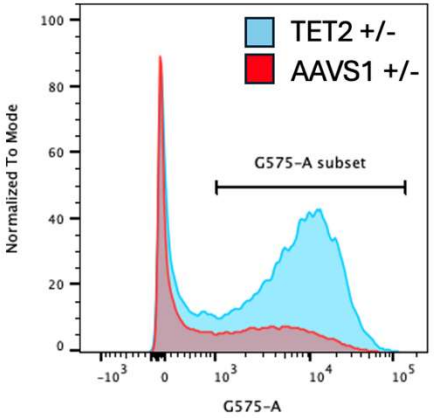
In-vitro data of TET2 CHIP macrophages

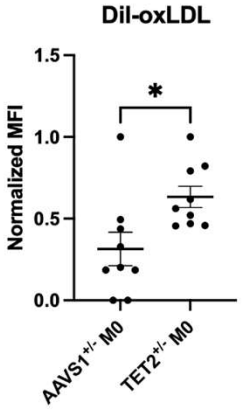
Work of Dr. Shaunak Adkar (STANFORD)











Conclusion: TET2 CHIP status in human macrophages is associated with increased inflammation, and uptake of LDL- and ox-LDL-cholesterol *in-vitro*.

STANFORD – Collaboration with Dr. Adkar / Prof. Leeper / Prof. Jaiswal

CONCLUSION

Summary & Conclusion

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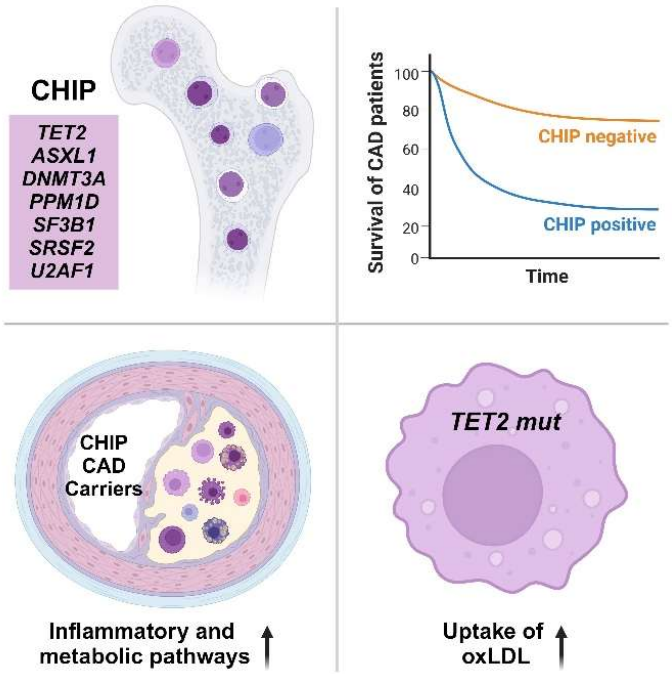
- CHIP is the strongest (modifiable) **CV risk factor** – driven by inflammation
- We established the **largest single center CHIP-CAD cohort worldwide**
- **CHIP is common, 1 out of 3 CAD** patients is **CHIP positive**
- **7 individual CHIP mutations were associated with mortality at VAF ≥2%**
  (ASXL1, DNMT3A, PPM1D, SF3B1, SRSF2, TET2 and U2AF1)
- We visualized **CHIP mutated leukocytes in human atherosclerotic plaques** (MutaFISH)
- **TET2 CHIP** status was associated with **upregulation of inflammatory and metabolic pathways** including lipid metabolism, and an aggravated **atherosclerosis** phenotype including **plaque instability** in MISSION
- **TET2 CHIP** affected **macrophages** were associated with **CAD and CAD complexity** in STARNET
- **TET2 CHIP** affected macrophages showed **increased LDL and ox-LDL-uptake** *in-vitro* (Dr. Adkar)

Clinical perspective: It appears likely that **TET2 CHIP** mutation carriers **might particularly profit from anti-inflammatory therapy as well as from aggresive lipid lowering treatment** strategies.

Prospective Studies



CADPT15A12201
Phase IIa Trial (RCT)
Started Q1/2024

IL1b and IL18 antibody in CHIP CAD patients with prior MI (n=32)

12 weeks

Surrogat outcome

CANCHIP (PI TUM)
Phase III Trial (RCT)
Starting Q3/2025?

Canakinumab (IL1b) in CHIP CAD patients (n=2000)

Event driven

Clinical events

Deutsches CHIP Register e.V.

Technische Universität München

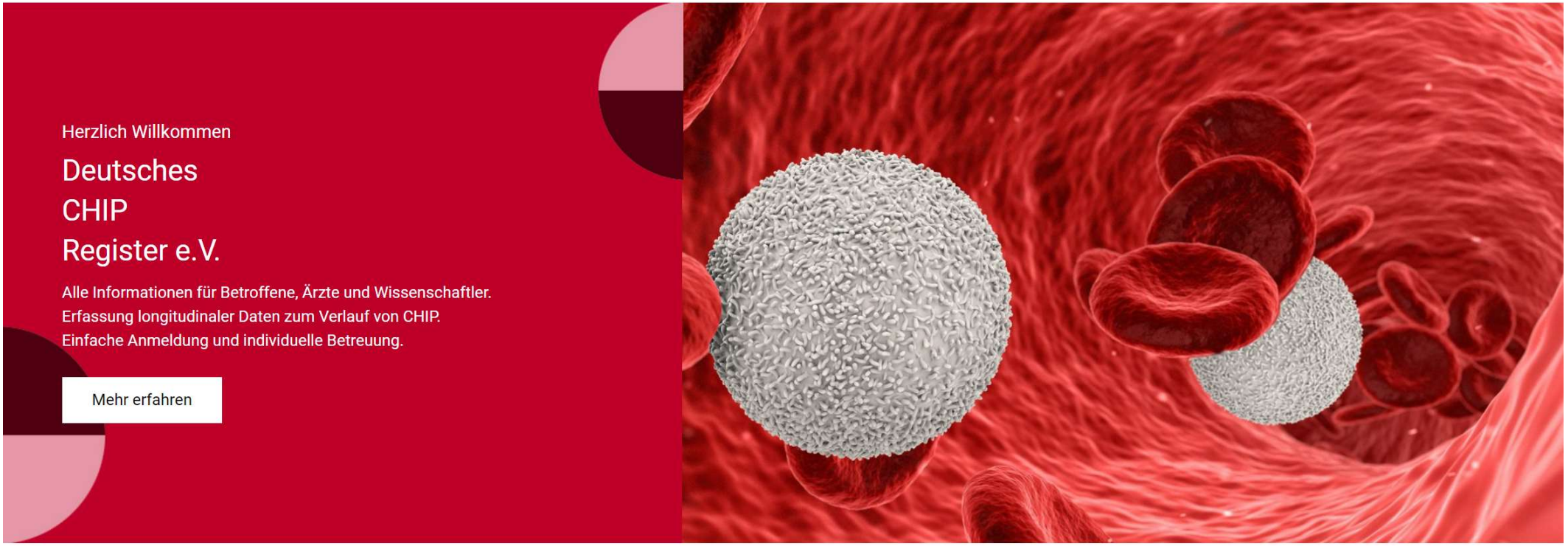
Datenbank Informationsportal Vernetzung

Über uns Kontakt Partner Deutsch Englisch

Deutsches CHIP Register

Home Für Betroffene Für Ärzte & Forscher

Anmeldung



Thank you for your attention!

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Deutsches CHIP Register
DZHK DEUTSCHES ZENTRUM FÜR HERZ-KREISLAUF-FORSCHUNG E.V.
Munich Heart Alliance
Leducq Foundation
Deutsches Herzzentrum München