TAXINOMISIS – a multidisciplinary EU project on stratification of patients with carotid artery disease

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STROKE RISK & CAROTID DISEASE
CAROTID DISEASE

- 50% reduction of lipid-rich plaques and intraplaque haemorrhage in symptomatic and asymptomatic carotid lesions
- Among all plaques with vulnerable phenotype only a very small proportion of them cause events
- Vulnerable plaques can lose their vulnerable characteristics while stable plaques can become vulnerable over time depending on exogenous factors
- Improved patient stratification has the potential to decrease the costs for management and treatment
NEW PROJECT

HORIZON 2020

TAXINOMISIS
NEW PROJECT - TAXINOMISIS

- The overall purpose of TAXINOMISIS is to provide novel disease mechanism-based stratification for carotid artery disease patients to address the need for stratified and personalised therapeutic interventions in the current era.
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LEADING VASCULAR SURGEONS
Endotypes

- Mathematical and systems medicine approaches for joint modelling of multiple omics and other datasets will be used to identify common latent variables that can be used to cluster plaque and plasma patient samples into biologically and clinically relevant disease subtypes (endotypes).
Disintegration of disease phenotypes into endotypes will be achieved through three major levels of resolution:
Multi-scale modeling of atherosclerosis

1\(^{st}\) level: 3D reconstruction of arteries

2\(^{nd}\) level: blood flow, LDL and mass modeling

3\(^{rd}\) level: Plaque growth modeling
Multiscale models

- The following retrospective will be used for the multiscale models under preferably more than one time points (BL, FU1, etc.):
  i. Protocol-based MRI or/and CT images
  ii. Data deriving from blood tests (HDL concentration, LDL concentration, Monocytes, Blood Pressure, Glucose, etc.)
  iii. Carotid Ultrasound (US) images
  iv. Biomarkers
HIGH VOLUME DATABASES

- Athero-Express Study
- Second Manifestations of Arterial (SMART) disease study
- Cardiovascular Risk in Young Finns Study
- Tampere Vascular Study
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<th>Partner</th>
<th>Cohort</th>
<th>Patients</th>
<th>Clinical follow up</th>
<th>Tissue</th>
<th>Imaging</th>
<th>Histopathology</th>
<th>Genomics</th>
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<th>Proteomics</th>
<th>Other datasets</th>
</tr>
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<tr>
<td>UMC</td>
<td>Athero-Express (AE)</td>
<td>n=2400 expanding</td>
<td>3 years</td>
<td>Carotid plaque, whole blood, plasma</td>
<td>Duplex US (n=1920) CT (n=2160) MR angio (n=960)</td>
<td>All, H&amp;E, CD68+, and aSMa+ IHC</td>
<td>GWAS (n=1443)</td>
<td>Methylyomics (n=488)</td>
<td>RNAseq of plaque (n=20)</td>
<td>2D LC-MSMS Yes (n=40)</td>
<td>Plasma-ELISA, Luminex for &gt;40 immunoproteins, many other biomarkers</td>
</tr>
<tr>
<td>UMC</td>
<td>Secondary Manifestations of Arterial Disease (SMART)</td>
<td>n=10000</td>
<td>10 years</td>
<td>N.A.</td>
<td>Duplex US (All) MRI angio (n=1300) MRI brain some</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A.</td>
<td>4 proteins in 1100 plasma EV samples</td>
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<td>TAUH</td>
<td>Young Finns Study (YFS)</td>
<td>n=2063</td>
<td>~35 years</td>
<td>Whole blood, plasma, serum</td>
<td>Duplex US (All)</td>
<td>N.A.</td>
<td>GWAS (n=2000)</td>
<td>Methylyomics: (n=190, two timepoints) miRNAomics: Whole blood (n=870, one timepoint) Serum (n=150, three timepoints)</td>
<td>Microarrays of whole blood (n=1600)</td>
<td>MS profiling of serum (n=44 cases with carotid plaque, n=44 controls, three timepoints)</td>
<td>Serum-ELISA, Luminex for ~50 immunoproteins, many other biomarkers Serum NMR metabolomics (n=2000 Three timepoints)</td>
</tr>
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<td>TAUH</td>
<td>Tampere Vascular Study (TVS)</td>
<td>n=103 expanding</td>
<td>N.A.</td>
<td>Plaque (33 carotid), blood cells, plasma, serum</td>
<td>N.A.</td>
<td>H&amp;E (All, Stary class.)</td>
<td>GWAS (n=83)</td>
<td>Artery/Plaque miRNAomics, (n=18)</td>
<td>Microarrays of whole blood (n=98)</td>
<td>N.A.</td>
<td>Serum NMR metabolomics, (n=56)</td>
</tr>
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<td>TUM</td>
<td>Munich Vascular Biobank (MVB)</td>
<td>n=1100 expanding</td>
<td>N.A.</td>
<td>Carotid plaque, serum</td>
<td>N.A.</td>
<td>H&amp;E (Most, plaque characterization)</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A.</td>
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<tr>
<td>USMI</td>
<td>IRCCS AUO San Martino-IST Genoa</td>
<td>n=288</td>
<td>&gt;6 years</td>
<td>Carotid plaque, serum</td>
<td>Duplex US (All)</td>
<td>H&amp;E, CD68+, aSMa+, MMP9+ IHC</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A.</td>
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<tr>
<td>NIVEL</td>
<td>Primary Care Database (NIVEL-PCD)</td>
<td>n=8000 with TIA n=18000 with stroke</td>
<td>7 years (2010-2016)</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A.</td>
<td>Medical history, as recorded by primary care doctor, including medication</td>
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Klinika za vaskularnu i endovaskularnu hirurgiju • Kliniki centar Srbije • Medicinski fakultet Univerziteta u Beogradu
Multiscale models

i. Protocol-based MRI
   a. TOF (time-of-Flight images for lumen reconstruction)
   b. T1W (T1 weighted images for outer wall reconstruction)
   c. Phase contrast images (used to calculate flow velocity)
   d. T2W and PDW images (for plaque characterization)
Multiscale models

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Multiscale models

**ii. Data deriving from blood tests**

a. HDL concentration
b. LDL concentration
c. Monocytes
d. Blood pressure
e. Glucose
f. Other indices that might be integrated in the final plaque growth model
Multiscale models

iii. Carotid Ultrasound Images (US)

a. Full velocity profile can be extracted
b. Grey-scale median: Median of the grey values of all pixels in the plaque image
c. Plaque type
d. Plaque area (mm²): Calculated by the imaging software using distance scale on the side of the image frame for calibration and the plaque area outlined by the operator
e. Juxtaluminal black areas (mm²): The juxtaluminal black area (JBA) (defined as the area adjacent to the lumen with pixels which after image normalization had a grey scale <25 without a visible echogenic cap) was outlined and the area automatically calculated.

A, Plaque with a juxtaluminal black area outlined in red without a visible echogenic cap, which is 10.5 mm² (JBA + ve ie ≥ 8 mm²)
B, Plaque with a juxtaluminal black area outlined in red without a visible echogenic cap, which is 3.2 mm² (JBA - ve ie < 8 mm²)
Multiscale models

- The following **prospective** data for multiscale models:
  
a. Medical record
b. Blood tests
c. Protocol-based MRI and/or CT imaging (for the full 3D reconstruction of the carotid artery of interest to validate the results of the plaque growth model that was applied on the respective baseline model)
d. Ultrasound Imaging
Preliminary Imaging Results

Multiscale models- UBEO-009

Areas of low WSS
Preliminary Imaging Results

Multiscale models- TUM-Med

Areas of low WSS
Risk stratification model
Disintegration of disease phenotypes into endotypes will be achieved through three major levels of resolution:
Lab-on-a-chip device for fast, easy-to-use, cost-effective detection of Single Nucleotide Polymorphism for genes controlling response to: statin, clopidogrel, warfarin, aspirin, dipyridamole or ticagrelor
Figure 23: TAXINOMISIS Pert Chart.