TAXINOMISIS

Multidisciplinary approach → stratification of patients with carotid artery disease

TAXINOMISIS plenary meeting
October 8-9, 2020, Athens

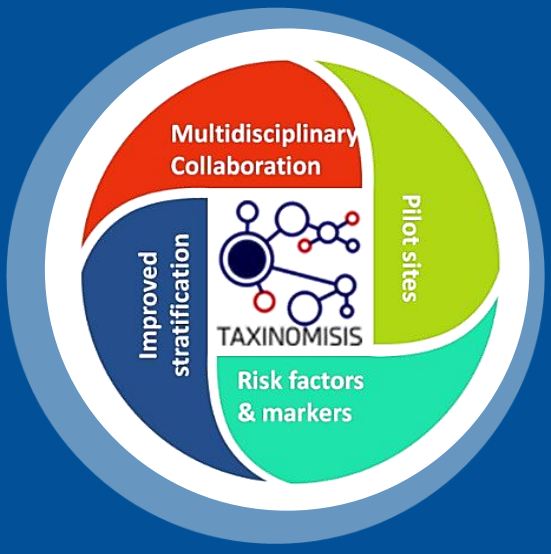
Newsletter 02 March 2020

TAXINOMISIS is a European Commission funded research project which aims to develop a new approach for the stratification of carotid artery disease patients.

TAXINOMISIS takes bold step beyond the state of the art unwinding the pathobiology underlying symptomatic plaques, discriminating distinct disease mechanism-driven states and biomarkers, and developing a multiscale risk stratification model.

TAXINOMISIS will deliver, as a main outcome, a software platform, which can perform the risk stratification.

TAXINOMISIS innovation capacity



Purposes

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.

Objectives

- → Investigate the causal relationship of the major pathways and factors identified in symptomatic carotid artery disease
- → Study disease phenotypes and disintegrate them into endotypes according to specific pathobiological mechanisms
- → Integrate a computational model and an agent based model of plaque progression in the risk stratification tool
- → Perform a test for determining the presence of single Nucleotide Polymorphisms and predicting drug response
- → Evaluate the risk model of carotid artery disease stratification in an observational multicentre clinical study
- → Present a cost-effectiveness analysis

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 755320

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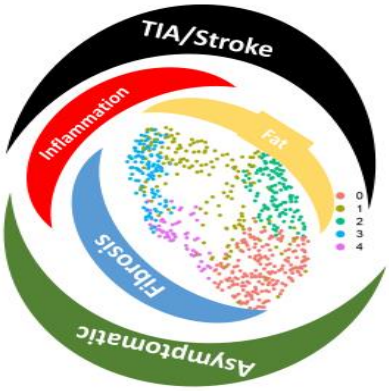
Project activities

Between the 21st and 26th month of the project, significant achievements have been accomplished in different work packages (WPs). Specifically:

Characterization of symptomatic and asymptomatic carotid atherosclerotic plaques lesions, and identification of risk and susceptibility factors through the exploitation of longitudinal cohort data and multiomics.

- The global expression profile of human atherosclerotic plaque by bulk RNA-seq has been characterized.
- Bulk RNA-seq data adds a layer of information on top of already existing histological information.
- Further analyses are undertaken and active discussion with later work packages.
- The human carotid atherosclerotic plaque at the single cell level using mass cytometry (CyTOF) and single-cell RNA sequencing (scRNA-seq) has been characterized.
- Circulating extracellular vesicle (EV) proteins and circulating ceramides have been measured to be able to assess their predictive ability for carotid artery disease risk.



Clusters found in the data

Disintegration of carotid artery disease phenotypes into endotypes through joint modelling of multiple omics datasets and systems medicine approaches

- Different layers of data were initially analyzed separately, assessing first transcriptomic data, protein measurements, and clinical data, looking at clustering patterns in the data.
- Vertical integrative analyses of the multi-layer -omics data was implemented.
- Initial results indicate that asymptomatic patients share plaque characteristics that are similar to patients presenting with amaurosis fugax. This gave rise to the hypothesis that amaurosis fugax may have another plaque related pathogenesis compared with TIA or stroke.
- Basic statistical analysis has been already conducted for each of the different datasets – available in TAXINOMISIS consortium - containing circulating biomarkers data.

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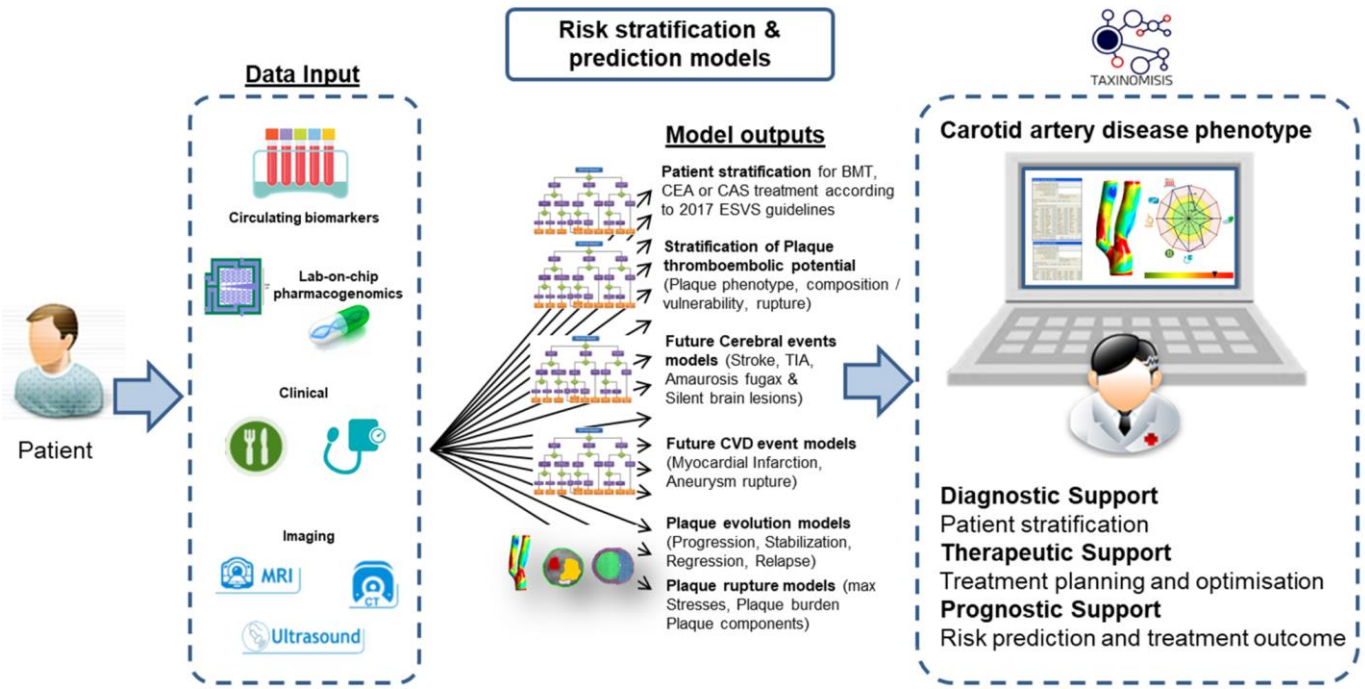
Risk stratification model

- The overall architecture of the TAXINOMISIS platform has been established.
- The first version of the computational model of plaque progression is under development using MRI and US data from the prospective clinical study, which incorporates new biological factors.
- The first version of the agent based model of plaque progression is under development including geometrical features from the computational model of plaque progression.
- The overall information flow of the Risk Stratification Tool is under consideration.



Schematic presentation of the proposed TAXINOMISIS Risk Stratification Model

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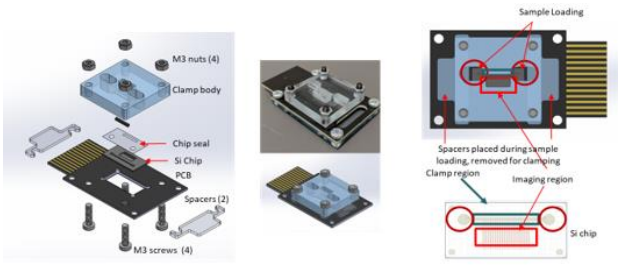
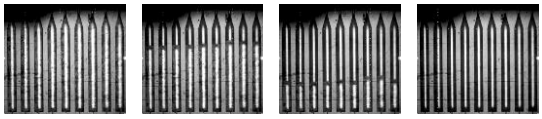
Pharmacogenomics analysis and development of a new lab-on-a-chip for further stratification of patients and personalization of medical treatment

Open-surface multicavity chips fabricated at IMEC were tested to assess the microfluidic flow and clamping solution for closing off the individual PCR reactors. Capillary-driven flow in the chip was confirmed and the efficiency of the clamping solution proven.
Miniaturized setup was built and tested using silicon chips.



Detailed overview of the clamping solution



Consecutive frames from the capillary water loading experiment

Dissemination, exploitation and commercialization activities

- The second version of the communication and dissemination activities is partly completed.
- The second version of the exploitation and innovation plan is being prepared.
- The definition of the market segmentation of TAXINOMISIS customers in relation with the potential beneficiaries is in progress. The aim is to create different cluster in the HC structures according their number of patients and the propension of buying different stage of TAXINOMISIS solution.

Structure/Solution	Full TAXINOMISIS solution provided to hospital and ambulatories	TAXINOMISIS solution provided which include the following: profiling tool and data stratification tool	Only profiling tool provided by TAXINOMISIS	Subtotal per dimension of structure
<=100 assisted patients	4%	6%	10%	20%
<=200 assisted patients	4%	6%	10%	20%
<=500 assisted patients	6%	9%	15%	30%
> 500 assisted patients	6%	9%	15%	30%
Subtotal per type of solution	20%	30%	50%	100%

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From research to the clinic: Evaluation of the new risk stratification tool in a prospective observational clinical study

An observational clinical study in patients with carotid artery disease is conducting, aiming to validate TAXINOMISIS system for risk stratification of carotid artery stenotic disease. For this purpose 300 patients in six European vascular centers with extracranial carotid artery stenosis >60% were recruited. Patient will be follow with 3 annual MRI examinations of brain and carotid arteries.

Study recruitment and e CRF form status

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Consortium

TAXINOMISIS encompasses a highly multidisciplinary group of researchers with remarkable track record and complementarity from 12 world-leading institutions of clinical and research excellence and 3 pioneering SMEs including:

- ✓ Medical experts
- ✓ Vascular surgeons
- ✓ Cardiologists
- ✓ Neurologists
- ✓ Biologists
- ✓ Software engineers
- ✓ Biomedical engineers
- ✓ Lab-on-a-chip experts
- ✓ Health research experts

TAXINOMISIS researchers are international leaders in their respective fields and have contributed to our current understanding of:

- the **clinical medicine surrounding carotid artery disease** (UMC, TUM, UBEO, USMI, FCRB, NKUA),
- **the molecular mechanisms** driving atherosclerosis in carotid and coronary arteries (UMC, TAUH, BRFAA, ZORA, USMI, UOXF),
- the **immuno-inflammatory processes involved** (UMC, BRFAA, USMI, UOXF, UBEO),
- the identification of **diagnostic markers and treatments** for cardiovascular disorders (TAUH, ZORA, IMEC, UMC, TUM, USMI, FCRB),
- **the development of new algorithms and simulation tools for atherosclerotic plaques and CVDs** (UOI, BIOIRC, END),
- **the development of risk prediction models** (UOI, BIOIRC),
- the design and production of **lab-on-a-chip devices** based on nanoelectronics (IMEC) and
- the provision of **retrospective data and cohorts** (NIVEL, TAUH, UMC)

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