

Meeting Minutes COST CliniMARK meeting September 2018
September 20-22, 2018
Medical Faculty, University of Belgrade, Serbia

- Intro Theo, WG leaders ought to be aware of the deliveries, at May 2019 we have to send a report to E-Cost. The white papers need attention and a plan is made in the meeting to accomplish these white papers. Extra budget for STMS and ITN grants has been realized for CliniMARK.

- **WG summaries**

WG1 - Sammar Marei

- Will now map technologies among the COST action members as review
- Immuno and MS. Multiplexing. New is Cap Elec, and electrochemistry.
- Add biomarkers for COPD so volatile biomarkers, exhaled breath, breath condensates.

WG2 - Peter Groenen

- Peter introduced the next meeting in Basel, Switzerland (28 and 29 March 2019). Perhaps combined with another conference about e-biomarkers, in development.
- Harald Mischak - discussion on making data available in databases accessible for researchers, a necessary condition for the white paper. In fact, these data bases are present EMBL (PRIDE) but how well are these data annotated for reanalyzing this data.

WG3 - Deborah Penque

- Revision of the WG3 tasks. Advances since Cascais meeting: Review on 'protein-biomarker research in COPD' published between 2016 (not included in Ongay et al 2016 review) and June 2018 was presented – manuscript submitted to *Expert Review of Molecular Diagnostics*.
- Criteria for selection of the most promising COPD biomarkers from those studies must be defined in order to select those for which BBP plans will be developed.

A discussion was about the content of this review, this review ought to be sent around for comments to the Core group/ Workgroup leaders at least for submission. In this way everyone can comment, and it can improve the manuscript. (Comment Theo)

WG4 - Florence Bietrix

- Clinimark website and logo developed
- Specific area for training on the CliniMARK website was added to it. CliniMARK partners are invited to send link/input on the training they are already offering regarding biomarkers validation to Andrea Wutte (andrea.wutte@bbmri-eric.eu). This is a first start in identifying training offering in EU and perform a gap analysis at a

later stage. Examples of training can be found <http://clinimark.eu/events.html>

- SharePoint sites for sharing of documents (internal) is fully functional and hosted on EATRIS servers. CliniMARK participants received login details and a training was provided through 3 open access webinars.
- For questions related to SharePoint, contact Laureboudaud@eatris.eu.

Round tables

• WG3+4 (15p)

- First define and focus on the Context of Use (or Purpose of Use). Is different for different stakeholders.
- Two papers thus far: Ongay et al 2016 and recent review manuscript COST CliniMARK 2016-2018. (Available at the password protected area of the CliniMARK website)
- Define the different fields that need biomarkers for COPD input from clinicians needed
- Workflow:
 - 1. Define the **Context of Use (COU)** in clinical area (e.g. exacerbation) + work backwards
 - 2. Focus on proteins
 - 3. Depending on the COU focus on biomarkers with mechanistic insight
 - 4. Map what is out there already + define added value needed
 - 5. Define additional options that must be part of the Biomarker Plan
 - Tissue evidence?
 - Assay in what matrix?
 - Minimally required specificity, selectivity, AUC of ROC?
 - 6. Then draft the biomarker plan
 - objective
 - clinical use
 - single/multiple biomarker
 - ultimate application
 - sample + data analytical plan
 - optimal analytical platform
 - optimal samples
 - power calculations
 - statistics
 - implementation plan
 - prototype assay
 - request input from clinicians
- Previous notes presented in the Cascais meeting by John Allinson on 'rationale for choice and expectations from clinical data' and by Rainer on 'COPD biomarkers clinical needs' were revised and have already been taking into account as criteria in biomarkers selection.

- A discussion was raised if this was the case. A careful reviewing of these manuscript is necessary to come to consensus. It was emphasized that clinicians ought to be involved in a more thorough way. In the next meeting more effort ought to be put in this part and is possible because we have different pulmonologists from different countries.
 - **Comments**
 - Replace p values with selectivity/sensitivity
 - Include mortality in criteria of selection.
 - Predicting exacerbations in COPD should be highest priority
 - Wide analysis of possible mechanistic effects.
 - Will need a few markers in combination. Start with list of candidates. Hard to define selection criteria (e.g. >500). Numbers are not the only condition
 - Markus: Define the COU well, what is really needed and what percentage of imperfection of the biomarker is allowed/ acceptable
- **WG2+4**
 - White paper (deliverable month 24, May 2019)
 - Action: Peter's WG will draft outline + assignments
 - Content
 - context of use
 - fit for purpose
 - data standards (including metadata)
 - statistics
 - Respected journal that is open (Clinical Chemistry, Proteomics)
 - Option to assign an STSM exchange
 - Action for WG4 Communication streams: how to disseminate the output white paper?
 - translate to training material
 - Skype with Laurens Baltzer (publisher at Karger)
 - Move to fully open access publications. Need different business model.
 - Digital biomarkers
 - Google, Apple: no openness of data
 - Apple smart watch ECG module approved by FDA
 - Get real world data
 - New journal
 - Combination of e-markers with more classical molecular markers
 - Metadata catalog
 - Discussion
 - Lack of standardisation of wearables and aps
 - Interaction with other publishers? Any standards in open access data.
 - Will be part of Biomarker meeting next year in Basel.
- **WG1+4 (Sammar Marei)**
 - Review to summarize protein biomarker techniques.

- An outline will be sent end October 31
 - size per technique, #references
 - table with details, SWOT?
 - Address technique + validity/robustness
 - Group detection methods,
 - Binders (antibodies, affimers, aptamers, lectines, etc.)
 - Detection methods (colorimetric, luminescence, electrochemistry),
 - Platforms.(ELISA, Olink, Simoa)
- Immunoassays
 - ELISA
 - IHC
 - Suna: POC, paper-based read-outs
 - Goran: Mesoscale
 - Florence: Luminex ring testing in other consortium (results very different)
 - Alain: SIMOA/Quanterix, Singulex
 - Ede: CE
 - Jan: electrochemically generated immunoluminescence, SPR (biorecognition)
 - Saara: DELFIA, RIA.
- Mass spec
 - LC-MS
 - MALDI
 - Mesoscale
- Tasks
 - Sammar + Alain: general outline/structure 31 Oct 2018
 - Saara + Theo: table + derived graphs 31 Oct 2018
 - Coordination
 - Immunoassays - ...
 - Mass Spectrometry - Jan
 - Electrochemistry - Jan
 - Time lines
 - 31 Oct 2018 structure + table
 - 31 Dec 2018 First draft
- Possible outline (further detailed at bar in hotel):
 - Review **'Analytical techniques for protein biomarker validation'**
 - Start point
 - Target audience
 - Bioanalytical scientists
 - Biomarker scientists
 - Clinical scientists
 - time point 0: what reviews already available
 - what kind of approach did we take (inclusion, exclusion)
 - Description Biomarker analysis workflow
 - Pre-analysis, Sample analysis, Data analysis, Post-analysis.
 - Two main sorts of protein biomarker methods:

- Binding assays (incl Electrochemical assays)
 - Start with ELISA
 - Solid phase
 - Binder
 - Detector
 - Assay system (flat surface, beads, paper)
 - Add table
- Mass spec assays
 - Sample prep material (LC, beads, etc.)
 - Affinity for prep
 - Analytical MS methodes (MALDI, QqQ, QTOF, IM MS)
 - Add table
- Comparison
 - 5-6 key aspects
 - E.g. established/emerging, speed, costs, resolution/data richness, dynamic range, robustness, matrix effects, multiplexing, quantitation, PoC option,
 - Describe in text + simple table
- Future perspectives
 - Self-monitoring (point of care), need higher sensitivity and specificity
 - MS can provide increasing details on proteins (PTMs), Ion mobility new dimension, need higher sensitivity and specificity
 - General flow from MS assay in biomarker validation to Binder assay in implementation/PoC
 - New types of binders

WG3+WG1

- John Allison, that joined the discussion by skype, has revisited which is necessary for the development of an analytical plan for a biomarker. He will send again his Rotterdam presentation to be available through the CliniMark website. Once the biomarkers are selected, John can start with the analytical plan for each of these selected biomarkers. The number of biomarkers may be around 4 at the most. For the choice of biomarkers, John suggests taking also into account those showing considerable fold-change differences between control and disease. COU for a biomarker is defined in the end of a validation/qualification process. WG4 will follow closely the development of these analytical plans

WG3+WG2

Summary session:

WG1 outcome

- Zanka: analytical validation is key. Key samples: blood and sputum.
- **Action:** Sammar + Alain to draft outline/structure

WG2 outcome

- Peter: manuscript review from WG2 to list current guidelines on clinical implementation protein biomarkers.
- **Action:** Peter and WG to draft outline/structure.

WG3 outcome

- Harald: write manuscript for COPD. Starting with Context of Use, desired outcome, candidate biomarkers. Get clinicians involved: Guy Brussels, Maria Torres, Tatjana Simic, Nick ten Hacken.
 - Deborah/Rainer drafted manuscript. Option to rewrite manuscript or draft second manuscript. For Deborah this is not an option, but it was concluded that the manuscript ought to be sent around for comment because there is discussion and if CliniMark is mentioned on this topic a thorough reviewing is part of the process. Andreas Scherer volunteered for investigating possible samples for validation.
 - Peter/Deborah: use evaluation of COPD Biomarker Qualification Consortium although it is focused on drug development.
 - **Action:** Harald + Eda, Makis - ask 3 clinicians for COU, then re-analyse current biomarker list. Involve Rainer (absent in Belgrade) also in this discussion.

WG4 outcome

- Alain:
 - **Action:** Andrea + Florence/Alain: communication plan for dissemination of white papers.
 - **Action all; Please send news items in this way the website is maintained well, also use the share point. Website looks very nice, let's use it to the best.**
 - **Send training offering available at your institutions on biomarker validation to be added to the website.**

Need for workshop/training for biomarker analytics

- Makis: 23-27 September 2019 Training planned.

Skype lectures

- Debbie Merrill
 - Pro-Active, approved by EMA 2016. Activity measure with e-diary.
 - 3 cohorts
 - ECLIPSE (GSK), tried but cannot replicate outcome from that study.
 - COPD Biomarker Qualification Consortium. Started 2010. Starting point was based on the need for new biomarkers to be applied to disease activity - in early- phase drug trials (Vestbo & Rennard 2010). Current selected biomarkers
 - Constant work rate exercise. 10.000 subjects, for submission to FDA.
 - Blood Eosinophiles for stratification
 - sRAGE for emphysema stratification
 - CAT (COPD assessment test)
 - Plasma desmosine
 - Imaging - explorative for stratification

- Qualification process takes about 5 years from start to approval.
 - shorter by joint FDA/EMA applications
 - Restricted FDA resources (1st focus on drugs, 2nd biomarkers)
 - Fibrinogen – first biomarker qualified by FDA as prognostic for mortality/exacerbation (COU: patient stratification in drug development)
- Aim for panel, but first start with individual biomarkers.

Makis

- STSM
 - procedure. minimum 5 days, max 90 days. Available money is EUR 2500.
 - Report within 30 days, 500 words max each section. Host will provide a letter of approval.
 - Eda Aydinoglu to Makis, review now submitted to Expert Review of Molecular Diagnostics (<https://www.tandfonline.com/loi/iero20>). File available in password protected area of CliniMARK site.
 - Suggest new STSMs. Spend before 30 April 2019.000
- ITC (inclusiveness target countries) conference grants
 - only for targeted countries: Albania, Bosnia-Herzegovina, Bulgaria, Cyprus, Czech Republic, Estonia, Croatia, Hungary, Lithuania, Latvia, Luxembourg, Malta, Montenegro, Poland, Portugal, Romania, Slovenia, Slovakia, the former Yugoslav Republic of Macedonia, Republic of Serbia and Turkey.
- Training/workshop Sept 23-27, 2019, Spetses Hotel, Greece
 - 21 speakers, 12 from CliniMARK.

Bischoff Rainer, Brun Virginie, Caceres Eva, Groenen Peter, Köks Sulev, Mischak Harald, Oliver Begona, Penque Deborah, Van Gool Alain, Vlahou Antonia, Wutte Andrea, Zoidakis Jerome.