CTC Technologies Meeting: Minutes on Discussion Points

1. Organization of the CTC technologies group:

Nikolas Stoecklein:

- We hope some of you will be interested in chairing/organizing subgroups within the technology working group but also within the CTC technology group specifically. If so, please give us feedback.

2. Working towards accreditation and reimbursement:

Evi Lianidou:

- ISO certification is elaborate. ISO process is therefore only sensible for clinically useful assays.

Michael O'Brien (ANGLE):

- This year, ANGLE has set up two clinical labs, one in the UK and one in Pennsylvania, US. These are primarily focusing on providing GCLP compliant CTC analysis services to pharma clinical trials. The results will not be for patient management. ANGLE's longer term goal is development of clinical tests for patient management – which would then require CLIA accreditation or ISO15189 certification for the tests and our laboratories.

Paul Hofman:

- Importance of selecting the right technologies for ISO certification/accreditation, i. e., the assay that clinicians will actually use.
- Accreditation process might be dependent on the specific countries regulatory bodies.

Catherine Alix-Panabières:

- Agrees that for accreditation of a clinically relevant assay, ISO is not mandatory to ensure reimbursement (at least in France). However, once an assay has been accredited, ISO might be nice to have.

Evi Lianidou:

- ISO certification process is highly homogenous across countries as it is centrally regulated.
- Importance of distinguishing between ISO certification and national accreditation.

Patrizia Paterlini-Brechot:

- Importance of involving manufacturers in ISO process as otherwise buffers and protocols may become outdated.

Tim Pitfield (Menarini Silicon Biosystems):

- Two laboratories offering lab services, one based on the US east coast (CLIA certification) and one in Bologna working toward ISO certification. Primarily for CellSearch enumeration.
- Menarini Silicon Biosystems also provide quality assurance kits for testing of the CellSearch regarding enumeration.

- Regulatory environment is changing in June 2022 across Europe (CIVD framework – more stringent testing around CE mark). Point to consider if you want your lab in the ISO framework.

Klaus Pantel:

- Please give feedback to Evi on whether you would be interested in joining the ISO framework with your lab/company and what are the potential bottlenecks in your perspective that have to be overcome.

3. <u>Ring trials and technology assessment:</u>

Nikolas Stoecklein:

- Focus on how we can continue work from CANCER-ID, compare technologies and include other cancer entities beyond breast and lung cancer.

Klaus Pantel:

- Ring experiments might be of especially high interest to providers of new CTC technologies that want to assess where they stand in the field in terms of reproducibility and yield etc. They are an objective way of testing the assays proficiency, independent of single groups and publications and therefore a strong indicator of performance. “ELBS guided tests” could become a valuable label in the field. Research groups are open minded, interested in making protocols work and without bias towards a specific technology. Ring trials could therefore be an element of financial support.
- Also, providers receive feedback on how protocols perform and where common errors are made, leading to fluctuating results. This process can be beneficial for both sides.
- Developers should send an email to Klaus, Evi and Nikolas to demonstrate their interest and current status of development (protocols etc.). We will collect the people who are open to such an effort and initiate a collaboration. In the past this meant that the interested labs received the technology, protocols and training from the provider.

Wim Ammerlaan (IBBL):

- IBBL is generally open to continuing the CANCER-ID working relationship in ELBS.
- CTC PT panel no longer entails the CANCER-ID lines but a local T18 line (not fully characterized). Further characterization can be provided. However, need to determine under which budget the pricing elements would fall (not out of own budget).

Leon Terstappen:

- Offer of characterizing the IBBL cell line to the same extent as in CANCER-ID.

Klaus Pantel:

- ELBS will find out the legal restrictions on distributing cell lines.

Rui Neves:

- Regarding the cell lines, possibly it would suffice for lines to be shipped in fixed state, without possibility of culture. The intent is on sharing samples and not cell lines.
- Providing and characterizing adequate cell lines could be the responsibility of the companies?

Evi Lianidou:

- Encourage companies that wish to develop reference materials for cells, to do so. Similar to horizon standards in plasma, cell-based reference material would be in high demand.

Krystyna Nahlik (LGC Seracare):

- Interest in moving into the cell-reference level. However, still early stages as it is very complex. Would be highly interested in specific requirements (cancer entities, size, mutations, markers etc.) required by trials.
- Leon Terstappen: Maybe Tim Pitfield has experience to share, as CellSearch already provides reference lines.

Nicolò Manaresi (Menarini Silicon Biosystems):

- Silicon Biosystems might be able to provide single cell controls for genetic analysis on single cells. Would need to check the amount of validation work to be able to provide this kind of material. The generation of single cell controls is regularly done for internal developments and might be extended.

Klaus Pantel:

- Catherine and the UKE could possibly provide our internal CTC cell lines as they do not belong to ATCC.
- A critical point of flexibility in technological standardization is the read out. What efforts are there to standardize read-out?

Leon Terstappen:

- The ACCEPT algorithm from research perspective is published. So far it is focussed on the DEP-Array and CellSearch (CS) and not applicable to other technologies
- Necessity of feeding the algorithm with images (at least 10,000 images to fill the database).

4. <u>Networking:</u>

Evi Lianidou:

- Importance of having a set date every month or every second month to keep up the discussion, work out deadlines, plans etc.
- This is a pilot meeting for CTC, ctDNA and other analytes will follow.

Tim Pitfield (Menarini Silicon Biosystems):

- This format is working very well, there are open and free discussions, would encourage more frequent meetings.

Markus Sprenger-Haussels (Qiagen):

- Qiagen agrees on a recurring meeting series to keep the calendars blocked and foster open communication to brain storm about technology evaluation and studies.

Klaus Pantel:

- We will make an action plan taking into consideration your feedback. Who is interest in what?
- Important next step would be to organize a meeting with the ELBS Clinical working group. Need to get input from clinical collaborators. Where are the applications that our clinical members are enthusiastic about for CTCs and ctDNA?

- We need to know from the clinical side on which targets we want to focus on (HER2, ARV7, PDL1, etc.). Our developments need to be closely in line with what is needed in the clinics.
- Next questionnaire should include clinical aspects to find a common denominator and zoom in on which questions we should start with by the second half of this year.

Nikolas Stoecklein:

- Importance of connection with other groups but also keeping focus on CTC technology from technical point of view.

Evi Lianidou:

- We should set up very specific goals for 1-2 markers for next year within our upcoming calls.

5. <u>Additional ideas and comments:</u>

Klaus Pantel:

- A very promising development is the use of artificial intelligence in imaging analysis. Many groups (including ours) have a wealth of CTC images in some format on our computers (not only for CellSearch but from other technologies). Maybe it would make sense to have subgroup focussing on image analysis?

Amin El-Heliebi:

- An open access databank of CTC images similar to sequencing data would be beneficial. Images could be pooled by the consortium. Image standards would need to be decided upon.

Galatea Kallergi:

- Very interested in sharing image pools and discussing actual patient samples (not only cell lines) to find consensus. What is characterized as a cancer cell?

Klaus Pantel:

- Raising the issue of antibodies, not all are equally good. We should think about comparing and testing different keratin antibodies. The issue is not fully solved and is a key instrument of CTC read out. Will think about how we could best compare antibodies to find out how complementary or redundant they are, maybe even on actual patient samples.

Leon Terstappen:

- Caveat: Keep in mind that you need to screen a lot of samples to decide on Abs (min. 100) to see differences. Not trivial endeavour.
- Possible solution: CellSearch samples which were stained for other markers, e.g. HER2 to find CK neg. cells. This could be done relatively quickly for markers such as PDL1 and others with existing datasets and image archives.

Nikolas Stoecklein:

- We will assess in the next questionnaire which Abs are used (if non-standardized commercially available assays are used).
- Anybody who has a specific interest and would want to initiate a working group is welcome to bring this forward. Please write us and we can help you organize this.