COST ACTION CA17118 - IDENTIFYING BIOMARKERS THROUGH TRANSLATIONAL RESEARCH FOR PREVENTION AND STRATIFICATION OF COLORECTAL CANCER (TRANSCOLOCAN)

Working group 1 participant duties

- Align with the scientific objectives of the Action's working group (see below).

- Participate in the working group activities and sign attendance lists.

- Contribute actively to the development of the work plan (see below).

- Develop guidelines/recommendations for the methodologies used in the working group.

- Foster and exchange knowledge, bring interdisciplinarity and create synergies within the working group.

- Remain open to new groups and be inclusive with groups with less capacity.

- Provide training to early-career and less capacity investigators.

- Aim towards FAIR data stewardship, i.e. making data Findable, Accessible, Interoperable and Reusable through tools such as OpenClinica, TranSMART and cBioPortal (https://health-ri.org/).

- Use results as input for future market applications.

- Disseminate the Action's working group to help expand the network and their results to society.

- Comply with COST rules (Vademecum).

- Open an eCOST profile (https://e-services.cost.eu/user/login) and submit expenses through it. - Overspending is not permitted and non-expensive options are required. Being careful with the Action's expenditure permits more participants to attend activities. As examples, low-cost flights are advised and accommodation should be just comfortable.

- Answer eCOST invitations to events promptly. A time limit of 2 weeks will be set to accept or decline. Unanswered invitations will be eliminated.

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Work plan - Working Group 1. Disease risk profiling

This WG will use low-penetrance germline genetic variants for CRC, microbiome characterization, epigenetics, metabolomics and environmental factors to model disease risk and apply it to better select individuals eligible to be screened for CRC or advanced adenomas.

Objectives

- To construct a CRC risk model using low-penetrance germline genetic variants, microbiome characterization, epigenetics, metabolomics and environmental factors.

- To improve the current CRC screening strategies by using the new CRC risk model.

Tasks

- To genotype individuals for germline genetic variants for CRC and methylation markers.

- To gather environmental data for individuals to be analyzed such as age, gender, family history, alcohol, diet, weight and exercise habits.

- To characterize a gut microbiome profile that can be used to identify individuals at risk of CRC.

- To typify a metabolomics profile that can be used to identify individuals at risk of CRC.

- To produce the CRC risk model calculation for analyzed individuals and evaluate it.

- To pilot the risk model in country-specific CRC prevention programs, and to evaluate its performance and acceptability.

- To evaluate the incorporation of the risk model into large-scale CRC prevention programs, with a focus on health economics, and propose modifications to screening based on risk score.

- To develop a consensus model and adopt consistent measures of CRC screening performance across the consortium.

- To report to the bodies and individuals involved in planning, funding and running CRC prevention programs with the aim of introducing the risk score into clinical practice.

- To increase awareness of the importance and usefulness of CRC screening programs for CRC prevention by actively involving patient associations.

Activities

Dedicated WG meetings will take place (1-2 per year). Workshops on the field will be included during meetings. A training school will be committed to the topic of risk profiling. Inter-laboratory exchanges in the form of STSMs are also envisioned especially for young researchers. A tight monitoring of the WG activities will be ensured by a strong WG committee.

Milestones

- Gut microbiome profile linked to CRC/advanced adenomas.

- Metabolomics profile linked to CRC/advanced adenomas.

- CRC risk modeling.

- Improvement of CRC screening programs.

Deliverables

- Research publications regarding microbiome, metabolomics profiling and CRC risk modeling.

- Software and protocols for CRC risk modeling.

- Guidelines for CRC screening.

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Working group 2 participant duties

- Align with the scientific objectives of the Action's working group (see below).

- Participate in the working group activities and sign attendance lists.

- Contribute actively to the development of the work plan (see below).

- Develop guidelines/recommendations for the methodologies used in the working group.

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- Provide training to early-career and less capacity investigators.

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Work plan - Working Group 2. Non-invasive biomarkers

It will apply state-of-art liquid biopsies for the detection and characterization of CTCs, ctDNA, tumor-derived exosomes and TEP, and test diagnostic value for adenomas and early-stage CRCs.

Objectives

- To establish a set of validated standard operating protocols (SOPs) that can be used to assess circulating biomarkers from patients with CRC and adenomas.

- To apply liquid biopsy SOPs to improve CRC screening, diagnosis, and monitoring.

Tasks

- To evaluate different systems and protocols for detection and characterization of CRC and adenomas CTCs, ctDNA, exosomes and TEP.

- To develop SOPs for detection of CRC and adenomas CTCs, ctDNA, exosomes and TEP.

- To create an infrastructure for multi-center trials and trainings to ensure compliance and performance of SOPs and to set criteria for assessing quality of clinical samples.

- To detect and characterize CTCs, ctDNA, exosomes and TEP in a multi-centre setup in defined sets of patients with advanced adenomas and CRCs, adenomas and healthy controls.

- To set quantitative criteria for classification and stratification of clinical samples.

- To compare data from CTCs, ctDNA, exosomes and TEP with clinical information derived from conventional diagnostic tools.

- To evaluate individual and multiple blood-based biomarkers for CRC diagnostic and monitoring.

- To evaluate the value of blood-based biomarkers as companion to the existing conventional diagnostic tools.

Activities

Dedicated WG meetings will take place (1-2 per year). Workshops on the field will be included during meetings. A training school will be committed to the topic of non-invasive biomarkers. Inter-laboratory exchanges in the form of STSMs are also envisioned especially for young researchers. A tight monitoring of the WG activities will be ensured by a strong WG committee.

Milestones

- Comparison of a pre-defined set of technologies and protocols for detection and characterization of CRC and adenomas CTCs, ctDNA, exosomes and TEP.

- Establishment of consensual SOPs for detection and characterization of CRC and adenomas CTCs, ctDNA, exosomes and TEP.

- Multi-centre comparison of SOPs.

- Establishment of criteria and cut-offs to classify samples according to their tumor content.

Deliverables

- Research publications regarding detection and characterization of CRC and adenomas CTCs, ctDNA, exosomes and TEP.

- SOPs for the detection of CRC and adenomas CTCs, ctDNA, exosomes and TEP.

- Guidelines for the inclusion of liquid biopsy for the diagnostic and follow-up of CRC.

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Working group 3 participant duties

- Align with the scientific objectives of the Action's working group (see below).

- Participate in the working group activities and sign attendance lists.

- Contribute actively to the development of the work plan (see below).

- Develop guidelines/recommendations for the methodologies used in the working group.

- Foster and exchange knowledge, bring interdisciplinarity and create synergies within the working group.

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Work plan - Working Group 3. Tumor profiling

WG3 will focus on the genomic, epigenomic and transcriptional profiling of colorectal adenomas and carcinomas in a multiregion analysis fashion in order to identify novel biomarkers with prognosis and predictive value for CRC patient stratification.

Objectives

- To generate genomic, epigenomic and transcriptional profiling of adenomas and CRC.

- To integrate the data generated in this section with clinical features to identify new biomarkers for prognosis and prediction of treatment response.

Tasks

- To assess the mutational profiling and the genomic copy number alterations in early colorectal lesions and carcinomas using multiregion whole exome sequencing.

- To identify the methylation patterns by multiregion analysis which define the tumor sequence from adenoma to carcinoma.

- To perform single-cell RNA sequencing to decipher affected molecular and cellular pathways.

- To integrate the genomic and transcriptomic data with ITH and the patient clinical output.

- To generate a gene panel for cancer progression and perform ultra-deep sequencing in the bulk of the advanced adenomas.

- Tools to trace tumor evolution and assess the ITH based on the –omics data generated in this WG.

- Patient-derived xenografts and single-cell cloning to reproduce *in vitro* the primary tumor ITH.

- To correlate the tumor profiling with the germline variants and the microbiome present in each patient obtained in WG1.

Activities

Dedicated WG meetings will take place (1-2 per year). Workshops on the field will be included during meetings. A training school will be committed to the topic of tumor profiling. Inter-laboratory exchanges in the form of STSMs are also envisioned especially for young researchers. A tight monitoring of the WG activities will be ensured by a strong WG committee.

Milestones

- Identification of biomarkers involved in the adenoma-to-carcinoma transition.

- Deciphering the genomic make up of advanced adenomas.

- Utilization of ITH as a prognostic predictor.

- Patient triage based on cancer genomics.

Deliverables

- Publication of the adenoma and carcinoma genomic profiles and their associated transcriptomic signatures in high profile journals.

- Tools to delineate tumor evolution.

- Therapeutic impact of ITH.

- Bench-to-bed transferability of biomarkers for prognosis and treatment response prediction.

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Working group 4 participant duties

- Align with the scientific objectives of the Action's working group (see below).

- Participate in the working group activities and sign attendance lists.

- Contribute actively to the development of the work plan (see below).

- Develop guidelines/recommendations for the methodologies used in the working group.

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Work plan - Working Group 4. Functional genomics and therapy

This WG will functionally validate candidate genetic variants from germline or tumor studies by using cutting-edge approaches such as CRISPR-Cas9 gene editing. On the other hand, it will conceive novel routes to CRC therapy including immunotherapy.

Objectives

- To link unequivocally genetic variants with an altered gene function or pathogenicity.

- To develop treatments for metastatic CRC more efficient and with less adverse effects.

- To develop immunomodulatory strategies sensitizing CRC not currently amenable to immunotherapy.

- To optimize the combination of immunotherapy with current (neo-)adjuvant therapies.

Tasks

- To select the germline and somatic candidate genetic variants to be validated.

- To perform gene editing for the selected genetic variants by using CRISPR-Cas9 and reintroduce them in cell cultures.

- To study the alteration of cellular processes and the specific gene function in the transfected cells, comparing the studied genetic variant and their wild type counterpart.

- To assign pathogenicity to genetic variants if an alteration is detected in previous studies.

- To use 3D and xenograft models mimicking the *in vivo* CRC tissue for functional analysis.

- To define actionable biomarkers that explain resistance to checkpoint blockade in patients with mismatch repair deficient CRCs.

- To demonstrate the application of neo-antigen targeted therapies in low mutation load CRC.

- To identify mechanisms circumventing the activation of immune responses as a result of widespread chromosomal instability.

- To demonstrate the applicability of immunotherapy in the context of neo-adjuvant therapy in rectal cancer to improve response rates.

Activities

Dedicated WG meetings will take place (1-2 per year). Workshops on the field will be included during meetings. A training school will be committed to the topic of gene editing. Inter-laboratory exchanges in the form of STSMs are also envisioned especially for young researchers. A tight monitoring of the WG activities will be ensured by a strong WG committee.

Milestones

- New genetic variants involved in germline predisposition to CRC.

- New somatic genetic variants involved in CRC progression.

- Novel improved therapies for metastatic CRC.

Deliverables

- Research publications about new pathogenicity links for genetic variants and their involvement in germline or somatic CRC predisposition, and about novel CRC immunotherapies.

- Protocols for CRISPR-Cas9 gene editing.

- Guidelines for functional evaluation of candidate gene variants by gene editing.

- Optimized pipeline for neo-antigen screening in CRC patients.

- Clinical protocols for the introduction of immunotherapy in (neo-)adjuvant treatment setting.