Modulo richiesta assegno

TUTOR	**Luigi Ricciardiello**		
TITOLO DEL PROGETTO			
Prevention of colorectal cancer linked to alterations of WNT and mTOR signals through the use of bioactive compounds: effect on organoids and intestinal microbiota of patients with FAP and colorectal cancer			
ASSEGNO FINANZIATO DA PROGETTO COMPETITIVO *(barrare la casella corrispondente)*	X SI	☐ NO	*Punti*
SE IL FINANZIAMENTO È COMPETITIVO L'ENTE FINANZIATORE	AIRC IG 2018 ID 21723		
PROGETTO/ATTIVITÀ A SCOPO COMMERCIALE *(es. sperimentazione profit)*	☐ SI	X NO	
CARATTERISTICHE DEL PROGETTO (*biomedico/osservazionale/clinico-interventistico/multidisciplinare*)	Multidisciplinare		
STATO DI APPROVAZIONE DEL PROGETTO DA PARTE DEL COMITATO ETICO (*se necessario per il tipo di studio barrare o evidenziare la casella corrispondente*)	X Ottenuto	☐ Da ottenere	

DESCRIZIONE DEL PROGETTO *(max 800 parole)* — *Punti*

Background and hypothesis

Familial adenomatous polyposis (FAP), due to APC mutations, is associated with a high risk of developing colorectal cancer (CRC). The hyperactivation of Wnt/β-catenin and PI3K/mTOR, together with alterations in the gut microbiota are known to contribute to CRC development. Treatment with Rapamycin or with Eicosapentaenoic acid was able to reduce adenomas development in the Apc Min/+ mouse model of FAP. We demonstrated that EPA supplementation affects the gut microbiota composition in both inflammatory and sporadic backgrounds and that a combination of EPA, Epigallocatechin-3-gallate (EGCG) and procyanidins had strong mTOR inhibitors effect in CRC cells. However, individual inhibition of Wnt/β-catenin or PI3K/mTOR is associated with activation of the non-inhibited pathway, thus justifying a combinatorial approach targeting both pathways.

Hypothesis

We hypothesize that a combination of Rapamycin, Omega-3 and EGCG could be a valid chemopreventive strategy for Wnt-driven CRC.

Aims

The aims of the project relative to the Task 1 are:
1) To test the combined effect of Rapamycin, Omega-3 and EGCG on mTOR, Wnt pathways and oncogenic mechanisms in CRC cell lines and colonic organoids from FAP and CRC patients; 2) To characterize changes in the gut microbiome in FAP and sporadic CRC patients.

Methods

Aim 1 and 2): We will recruit 20 Fecal Immunochemical test positive (FIT+) subjects (controls), 20 FAP patients and 20 patients with sporadic CRC to evaluate the activation of Wnt/β-catenin and PI3K/mTOR pathways and the mutational profile of adenomas and cancers. We will characterize oral, fecal and mucosal microbiome signatures in all recruited subjects. The combination of Rapamycin, Omega-3 and EGCG will be tested on selected CRC cell lines and on colonic organoids derived from enrolled patients.

Expected results

We expect to find relevant differences in the microbiome structure, as well as in the activation of Wnt/β-catenin and PI3K/mTOR pathways in FAP and CRC patients compared with FIT+ control subjects. In addition, we believe that treatment with a combination of Rapamycin, Omega-3 and EGCG will have a synergic effect on Wnt/β-catenin and PI3K/mTOR, leading to a reduction of cell viability and proliferation.
Our data will establish new chemopreventive strategies in FAP and sporadic CRC patients and define microbiome changes associated with APC gene mutations which will be useful as predictive tool for CRC.

DESCRIZIONE DELLE ATTIVITÀ DELL'ASSEGNISTA (Description of the expected research activities) *(per i **nuovi** assegni: max 400 parole; competenze richieste, scansione temporale della formazione, scansione temporale dell'attività, obiettivi primari e secondari)* *(per i **rinnovi**: max 600 parole – da integrare con la relazione dell'assegnista; formazione raggiunta, attività effettuata, obiettivi raggiunti/competenze acquisite, formazione ancora da acquisire (se pertinente), scansione temporale dell'attività durante il rinnovo)*	*Punti*

The grant is intended for a candidate who will fill a senior role. The winning candidate must have a masterdegree in:

- Molecular and Cellular Biology, Biology or Molecular and Industrial Biotechnology. For foreign applicants, equivalent degrees will be considered.
- Being in possession of a research doctorate, with an adequate scientific-professional curriculum in relation to the aims of the project, is preferable, but not essential.

Other skills / requirements of candidates:

- The candidate must have demonstrated experience in the last 3 years linked to laboratory activities, in particular with molecular and cellular biology techniques. The experience with animal and 3D culture models is preferable, but not essential.

In addition, the scientific production in peer-reviewed journals will be also preferred.

The winning candidate will have to supervise and carry out the following activities:

1) Collaborate in the procurement of biological samples derived from FAP, FIT + and CRC patients.

2) Carry out the isolation and propagation of intestinal organoids from FAP, FIT + and CRC patients.

3) To evaluate the basal activation level of the mTOR and WNT pathways on patient-derived tissues and organoids.

4) Evaluate the effect of Rapamycin, Omega-3 and EGCG on mTOR and WNT pathways and on markers of apoptosis and cell proliferation on patient-derived tissues and organoids.

5) Collaborate in the analysis of the oral, mucosal and fecal microbiota from patient-derived samples and in the characterization of microbial metabolites;

6) Collaborate in statistical analysis and data interpretation activities.

The time frame of the activities is divided as follows:

First semester: Continuation of the sample procurement, isolation and propagation of organoids. Evaluation of the basal activation level of patient-derived tissue pathways by immunohistochemistry, western blot and real-time PCR analysis.

Second Semester: Continuation of sample procurement, isolation and propagation of organoids. Evaluation of the chemopreventive effect of Rapamycin, Omega-3 and EGCG on the pathways of interest and on markers of apoptosis and cell proliferation. Analysis of the microbiota and microbial metabolites. Statistical analysis and data interpretation.

SE RINNOVO, SI RICORDA DI ALLEGARE ANCHE LA RELAZIONE DELL'ASSEGNISTA.

Scheda attività assistenziale (se prevista)

ATTIVITÀ / N. ORE SETTIMANA
Non prevista
AZIENDA SANITARIA PRESSO CUI SI SVOLGERÀ L'ATTIVITÀ
Non prevista

Si ricorda che, come previsto dagli Accordi sull'impiego nell'attività assistenziale dei Titolari di assegni di ricerca, sottoscritti tra l'Università di Bologna e le Aziende Ospedaliere di riferimento, una volta stipulato il contratto con il vincitore della selezione, il tutor deve consegnare alla Direzione Medica Ospedaliera la relativa modulistica, nella quale andranno riportate le attività qui segnalate.