## Appendice III - Scheda di sintesi del bando

**Avviso pubblico per la presentazione di progetti per attività di ricerca industriale e sviluppo sperimentale indirizzato a organismi di ricerca, 'bandi a cascata' da finanziare nell'ambito del Piano nazionale per gli investimenti complementari al PNRR (PNC, istituito con il decreto-legge 6 maggio 2021, n. 59, convertito dalla legge n. 101 del 2021), iniziative di ricerca per tecnologie e percorsi innovativi in ambito Sanitario e Assistenziale (Decreto Direttoriale n. 931 del 06-06-2022), progetto PNC0000003 - Anthem - AdvaNced Technologies for Human-centrEd Medicine finanziato con il Decreto Direttoriale 9 dicembre 2022, prot. n. 0001983 - CUP B53C22006590001**

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| **TITOLO** | Spoke 4 – Preclinical and clinical breakthrough theranostic and treatments for cancer dell'Iniziativa "Anthem - AdvaNced Technologies for Human-centrEd Medicine" progetto PNC0000003 - Bando a cascata per attività di ricerca industriale e sviluppo sperimentale indirizzato a organismi di ricerca |
| **INVESTIMENTO** | Piano nazionale per gli investimenti complementari al PNRR (PNC – Piano nazionale complementare), intervento "Iniziative di ricerca per tecnologie e percorsi innovativi in ambito sanitario e assistenziale" |
| **OBIETTIVO GENERALE** | Finanziamento di progetti di ricerca industriale e sviluppo sperimentale finalizzati allo sviluppo di prodotti, processi o servizi nuovi/migliorati. |
| **OBIETTIVO SPECIFICO** | Attività di ricerca e sviluppo sulla seguente tematica:<br>**Tematica A1 -** Development and implementation of advanced model systems based on the integration of omics approaches through artificial intelligence algorithms, capable of enabling the complete mapping of the biological characteristics of metastatic tumors in patients with metabolic dysfunctions: The project involves the development of an integrated biocomputational platform based on advanced experimental models capable of accurately reproducing the molecular and biological peculiarities of human metastatic tumors to predict their clinical aggressiveness in relation to different metabolic microenvironments. The development methods of the platform must include the use of omics strategies and artificial intelligence algorithms that will allow advanced computational approaches capable of processing molecular signatures with topographic annotation (for example, "genotype to phenotype"), metabolic, biological, and functional peculiarities obtained from experimental models in vitro, in vivo, ex vivo, and in silico capable of recapitulating the clinical complexity of metastatic tumors in different metabolic contexts. The initial phases of development and implementation of the project should be followed by a preliminary validation of the predictive/prognostic efficacy of the clinical profiling tools developed also at the basic and applied research facilities of the Anthem project partners.<br><br>**Tematica B1** - Production and analysis of radiobiological data for a deeper insight into the dose-effect relation in Flash therapy and BNCT<br>The possibility to assess a proper treatment planning for patients when new forms of radiotherapy (RT) are concerned stems from the capacity to predict the therapeutic effect as a function of the absorbed dose and to assess the effects in the surrounding healthy tissues.<br>New treatment opportunities come from novel techniques, which have demonstrated to produce a widening of the therapeutic RT treatment window, such as "FLASH radiotherapy" and "Boron Neutron Capture Therapy (BNCT)".<br>FLASH RT consists in delivering the prescribed dose at very high dose-rates, at least 100 times greater than those used in conventional regimes. This RT treatment produce the so-called |

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| | "FLASH effect", repeatedly observed in preclinical experiments, consisting of limited or absent radiation-induced toxicity on healthy tissue, including brain and cognitive preservation. Such an advantage would allow the delivery of higher doses to the tumor, with limited or no side effects on surrounding tissues and organ at risks. However, the physical and biological mechanisms still need to be still elucidated. In particular, preclinical experiments on Zebrafish and murine models will be necessary to better highlight the Relative Biological Effectiveness (RBE) ratio in case of FLASH irradiation, which is necessary in order to make a FLASH RT clinical transfer. In addition, a radiomic study, by using a molecular imaging approach, would represent a novelty in this field, permitting to identify radiomic features characteristic of the FLASH effect, by the imaging comparison of FLASH vs conventional treatments. Similarly, in BNCT, the dose is determined by the distribution of 10B in tissues. The charged particles released in the neutron capture have a range comparable to the average size of the cell, thus the capacity to obtain information on the micro-localization of boron at the subcellular level adds to the prediction power of the damage caused by BNCT when it is mediated with a specific borated carrier. An optimal boron biodistribution would ensure the therapeutic effect for a lower total absorbed dose. This leads to the necessity of measurements techniques able to detect boron inside cells and to use this information in proper models to express the photon-equivalent dose. This approach, based on experimental methods and computational simulation should also be able to assess the effectiveness of different borated formulation and different strategies to load them into tumour cells. In general, both in BNCT and Flash therapy, there is a strong need for radiobiological data aimed at understanding the effects due to a definite dose distribution. Irradiation of preclinical models with neutron, photon and proton beams must be carried out, with innovative biological assessments of the effects. Monte Carlo simulations such as Geant4DNA will be used to calculate precise dosimetry and understand the dose-effect relation. To this end, specific experiments may be organized for validation purposes. This call aims to promote a more comprehensive understanding of the dose-effect in new forms of radiotherapies and to generate knowledge that can be translated into the clinical practice, facing the challenge from the biological and physical points of view and using innovative methods.<br><br>**Tematica C1** - Preclinical assessment of dose-effect relation of proton and FLASH therapy in GBM vertebrate models<br>Proton beam therapy (PBT) is a particle radiotherapy with excellent dose localization that permits treatment of deeply localized tumors by administration of a high dose to the tumor while minimizing damage to surrounding normal tissues.<br>One of the applications of PBT and FLASH therapy is brain tumors (Peters et al., 2022). PT is preferred for patients because it reduces moderate to low doses to critical structures. However, as the population of long-term cancer survivors grows, incidence of late treatment related toxicities is becoming apparent.<br>To assess the effectiveness and safety of these novel radiotherapy approaches to target brain tumors, alone or in combination with other therapies, in vivo models are essential.<br>Among the vertebrate models, zebrafish have been widely used in radiobiology. Dose-effect studies have been performed with a range of radiation sources, including proton and flash therapy. At the same time, several models of endogenous and xenotransplanted tumors have been developed.<br>In this call, we aim to establish a protocol for assessing toxicity and effectiveness of proton and flash therapy in zebrafish models of brain cancer, which will include the use of advanced technologies, set up for use in small vertebrates, and established models of brain cancer. The experimental validation should include a set of biological information (survival, cardiotoxicity, cell death, tumor proliferation, DNA damage and repair, tumor migration and immune |

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<tr><td></td><td>responses) that can be easily applied to clinical practice. Ideally, a combination of the radiotherapy approach with specific drugs, already established or newly discovered in customized drug screens, could be included in the project.<br><br>Tematica D1 - The impact of GBM on microenvironment<br><br>To improve understanding and on the influence of GBM development on metabolic pathways of surrounding health cells, an in-depth study through a targeted metabolomics approach will be needed. In particular, the study should be focused on the determination of the metabolic changes induced by glioblastoma development on metabolism of surrounding cells using well established, reliable, reproducible techniques capable to quantify compounds of central metabolism. To this purpose, it is mandatory to evaluate changes in energetic metabolites (mono-, di- and triphosphate nucleotides, nucleosides, nicotinic coenzymes, coenzyme A derivatives, UDP derivatives, etc.) related to mitochondrial functions and major central metabolic pathways, as well as metabolites related to the function of different cell types and indexes of metabolic viability, such as N-acetylaspartate, will be required. In addition, to fully decipher the influence of GBM development on metabolism of surrounding cells, the study should support evidences on the possible molecular signals released by GBM and used to alter metabolism of neurons, astrocytes, glial cells. The metabolic pathways of target cells affected by GBM should be evaluated also in terms of gene and protein expressions, with particular emphasis on those processes involving mitochondrial functions (energy metabolism, compounds of the electron transfer chain, intermediates of the tricarboxylic acid, genes and proteins involved in the mitochondrial quality control. Additionally, the proposal should also focus to evaluate metabolism in an in vivo model of GBM in the Zebrafish. Through scientific publications in leading journals, the proponents should demonstrate their proven ability in the optimal preparation of biological samples for the analysis of high turnover metabolites, quantification of protein and gene expression, and determination of enzyme activities, as well as to perform the exact quantification of metabolites of interest (neurotransmitters, free amino acids, antioxidants, N-acetylaspartate, energy metabolites, etc.).</td></tr>
<tr><td>DOTAZIONE FINANZIARIA</td><td>La dotazione finanziaria del presente bando è di € 2.628.444,76<br>Dotazione per RI: € 525.688,95<br>Dotazione per SS: € 2.102.755,81<br>Percentuale quota Sud: 60% (€ 1.781.066,86)</td></tr>
<tr><td>AMBITO TERRITORIALE</td><td>Territorio nazionale</td></tr>
<tr><td>SOGGETTI AMMISSIBILI</td><td>Organismi di ricerca e diffusione della conoscenza</td></tr>
<tr><td>PROGETTI FINANZIABILI E INTENSITÀ DI AIUTO</td><td>Progetti di ricerca e prototipazione finalizzati allo sviluppo di prodotti, processi o servizi nuovi/migliorati che prevedano attività di ricerca industriale e/o sviluppo sperimentale (in forma singola o in partenariato). Ciascun progetto deve prevedere entrambe le attività in combinazione, comunque, destinando non meno del 30% dei costi allo sviluppo sperimentale.
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<tr><th>TIPOLOGIA DI SOGGETTO</th><th>ATTIVITÀ</th><th>INTENSITÀ MASSIMA DI AIUTO</th></tr>
<tr><td rowspan="2">Organismo di ricerca</td><td>RI</td><td>100%</td></tr>
<tr><td>SS</td><td>100 %</td></tr>
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<tr><td>DIMENSIONE FINANZIARIA</td><td>Minimo 200.000,00€ massimo 1.128.444,76 € di finanziamento per progetto</td></tr>
<tr><td>DURATA DEL PROGETTO</td><td>Massimo 24 mesi</td></tr>
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| **SPESE AMMISSIBILI** | Spese per progetti di ricerca collaborativa:<br>A) SPESE DI PERSONALE (30% dell'agevolazione totale)<br>B) COSTI PER STRUMENTI, ATTREZZATURE E LICENZE (minimo 50% costo totale progetto)<br>C) SPESE GENERALI (20% dei costi diretti ammissibili per il personale)<br>D) ALTRI COSTI DI ESERCIZIO (20% delle spese ammissibili di cui alle lettere a) e b) incluse le consulenze) |
| **MODALITÀ DI PRESENTAZIONE DELLA DOMANDA** | **Modalità:** La domanda di finanziamento potrà essere presentata dal Capofila del partenariato via PEC al seguente indirizzo: protocollo@pec.unict.it<br>**Tempi:** scadenza 28 aprile 2024 ore 23:59. Modulistica reperibile all'indirizzo: https://www.unict.it/it/bandi/ricerca-e-trasferimento-tecnologico/pnrr-bandi-a-cascata . |
| **FASI DELLA VALUTAZIONE** | a. Istruttoria formale<br>b. Valutazione di merito<br>Al termine della valutazione di merito approvazione della graduatoria dei progetti ammessi e non ammessi a finanziamento. |
| **RESPONSABILE DEL BANDO** | Dott.ssa Elvira Cardillo - Università degli Studi di Catania, Area della Ricerca<br><br>Eventuali domande di chiarimento in merito ai contenuti dell'avviso e dei relativi allegati possono essere indirizzate a mezzo e-mail all'indirizzo elvira.cardillo@unict.it |