Università degli Studi di Perugia

PNRR: consultazione per la raccolta di proposte progettuali

SCHEDA

Proponente della proposta progettuale	Prof. Antonio Macchiarulo
Dipartimento/Centro del Proponente/Coordinatore	Dipartimento di Scienze Farmaceutiche
Dipartimenti/Centri potenzialmente coinvolti	Dipartimento di Medicina e Chirurgia, Centro di Ricerca Emato-Oncologico (CREO), Dipartimento di Ingegneria
Eventuali collaborazioni pubbliche e/o private (riportare eventuali partner istituzionali/imprenditoriali coinvolgibili nell'idea progettuale	Università degli Studi di Firenze (CERM), Università del Piemonte Orientale, Università degli Studi di Torino, Università degli Studi "G. d'Annunzio" Chieti – Pescara, TESpharma srl, Claris Ventures, Galapagos.
Titolo (indicativo) della proposta progettuale	Integrated Strategies for the Design, Synthesis and Evaluation of Next Generation Immunotherapies.
Tematica/tematiche di prevalente interesse (max 300 caratteri spazi inclusi)	The proposal fits mission 4, component 2, thematic 1. Skills and know-how of research groups within the University of Perugia will combine with external public and private partners to design next generation small molecules for the development of personalized immunotherapies in precision medicine.
Grado di T.R.L di partenza (ove applicabile la scala TRL, descrivere il livello di maturità dell'ipotesi progettuale iniziale facendo riferimento ai gradi e alle declaratorie della scala TRL europea)	The proposal aims at providing new perspectives for an effective pharmacological modulation of selected immune checkpoint proteins including enzymes (e.g. IDO1), receptors (e.g. AhR) and membrane proteins (e.g. PD1/PDL1, CTLA-4) on the route to personalized immunotherapies. In this framework, inhibition of IDO1 activity, either alone or combined with the inhibition of additional immune checkpoint targets may lead to a more effective blockade of tumor immune-escape process in neoplasia and to an increase in response rates of patients on anti-tumor immunotherapy. Conversely, positive allosteric modulation of IDO1 by small molecules may prove beneficial for the therapeutic treatment of autoimmune disorders such as multiple sclerosis (MS), inflammatory bowel disease (IBD) and type I diabetes. The starting technology readiness level of the proposal is TLR 3, i.e. we already achieved the experimental proof-of-concept that small molecules (e.g. VIS110, VIS128, VIS329) are able to modulate IDO1 activity, exerting immune-adjuvant (VIS128) or immune-suppressive (VIS110, VIS329) effects on DCs. At the end of the project, we expect the achievement of a TLR 4, namely the validation of n.2 small molecules acting as immunoregulatory lead compounds in n.3 different animal models which include murine B16 melanoma model for cancer disease, murine DSS-induced model of acute and chronic colitis for IBD, murine experimental autoimmune encephalomyelitis for MD disease, either alone or in combination with other small molecules targeting other immune checkpoint proteins.
Sintesi (estrema) degli obiettivi e delle possibili ricadute nel territorio locale e/o nazionale (descrivere i principali obiettivi, i risultati attesi e eventuali impatti di ricaduta;	Design and synthesis of n.100 small molecule modulators of immune checkpoint targets. Characterization of physicochemical properties.

max 500 caratteri spazi inclusi)	Identification of n.50 active modulators of immune checkpoint targets by biophysical and cellular appraisals. In vitro and in vivo toxicology. Identification of immunomodulatory effects of n.9 active compounds in proof-of-concept studies using n.3 animal models. Genotyping studies for responsive patients. Creation of spin-off. Networking with pharmaceutical companies.
Costo complessivo del progetto (riportare in k-euro l'ordine di grandezza: 100 k-e, 500 k-e, ...)	2.000 k-e
Informazioni aggiuntive (riportare ogni informazione ritenuta utile a rappresentare l'idea progettuale: es. eventuali finanziamenti nazionali/internazionali già ottenuti, eventuali partenariati nazionali/internazionali già consolidati intorno all'ipotesi progettuale; eventuali attività di ricerca commissionata in partenariati pubblico/privati collegati all'idea progettuale; eventuali brevetti collegati; collaborazioni in atto da lunga data etc. – max 500 caratteri spazi inclusi)	The proposal originates from results of ERC-2013-AdG-338954, ERC-2017-PoC-780807-DIDO-MS, ERC-2019-PoC-899838-ENHANCIDO, and results from PRIN-2012S47X27 (MIUR). A patent application has been filed on related compounds (WO2019211783A1). The project has been presented in showcasing events: Biovaria 2019, Tech Share Day 2019, BioinItaly 2021. The project has attracted interest from Claris Ventures, an early stage biotech investor company, and Galapagos, a European commercial-stage biotech company.