PHYSICIAN SCIENTIST
LA MEDICINA INCONTRA LA RICERCA
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2026 Physician Scientist Call

AVAILABLE POSITIONS

Principal Investigator	SALVATORE DOMENICO
Institute of Affiliation	Università degli Studi di Napoli "Federico II"
Title of the proposed project:	Targeting thyroid hormone signaling to overcome cancer-related fatigue driven by tyrosine-kinase inhibitors
Short description of the project	Cancer-related fatigue (CRF) affects up to 95% of cancer patients and represents one of the main causes of reduced treatment adherence, dose intensity, quality of life, and survival. CRF is common in patients receiving tyrosine kinase inhibitors (TKIs). Despite its clinical relevance, the biological mechanisms underlying TKI-induced CRF remain poorly understood and preventive strategies are lacking. Our hypothesis is that TKI-induced CRF is driven, at least in part, by impaired thyroid hormone (TH) signaling within the brain. We and others have demonstrated that several clinically relevant TKIs inhibit type 2 deiodinase (D2), responsible for converting thyroxine (T4) into the active hormone triiodothyronine (T3). Since brain T3 availability largely depends on D2 activity, TKI-induced D2 inhibition may reduce local T3 levels and disrupt neural pathways involved in cognition, memory, behavior, and neuronal plasticity, all processes implicated in CRF. Preliminary studies from our Endocrinology Lab at Federico II University showed that TKIs inhibit D2 activity. Furthermore, RNA sequencing of mouse brain cortex after lenvatinib treatment revealed extensive transcriptional alterations affecting pathways related to cognition, synaptic plasticity, and neuronal function. Similar abnormalities have been described in models of defective D2 activity and can be improved by T3 supplementation. The project combines transcriptomic analyses, cellular models, animal studies, and a pilot clinical trial to determine whether impaired TH signaling contributes to TKI-induced CRF and whether restoration of T3 availability can reverse these alterations. Specifically, we will identify TKI-induced brain molecular signatures, evaluate rescue strategies in neuronal models, test thyroid hormone supplementation in vivo, and assess the impact of LT3 supplementation on fatigue and quality of life in patients receiving TKIs. This translational research may identify novel biomarkers and therapeutic approaches for CRF, ultimately improving treatment tolerance, quality of life, and clinical outcomes in cancer patients.
Main research area for the project	Cancer Biology
5 keywords for the project	Thyroid hormone – Endocrinology - Thyroid ca.

LAB INFO	
Main topic/s of the lab	Thyroid hormone metabolism, thyroid cancer

Short description of the lab activity	SPECIFIC AIMS Aim 1 Dissect the TKI-induced signature in the brain to identify potential targets linked to CRF. We hypothesize that TKIs alter brain signaling pathways related to CRF that overlap with TH signaling. We will analyze the transcriptomic changes following TKI exposure in the cortex, hippocampus, and cerebellum to identify pathways i) significantly affected by TKI treatment, ii) overlapping with TH-dependent signaling, and iii) potentially linked to CRF. To this end, we will compare RNA-seq profiles from the cortex, hippocampus, and cerebellum of mice treated with two clinically relevant TKIs (the antiangiogenic lenvatinib and the RET-inhibitor selpercatinib) with untreated controls, and identify shared transcriptome alterations. Next, we will analyze transcriptional changes in the same brain regions of hypothyroid mice versus controls, and assess overlaps with TKI-induced alterations. We expect to define a TKI-induced transcriptome signature to guide further analyses, that partially overlaps with TH signaling, and that may reveal candidate pathways for therapeutical intervention. If no major crosstalk with TH signaling is observed, these experiments will still identify biologically relevant TKI-induced pathways linked to CRF that can be tested in subsequent rescue experiments. Aim 2. Test whether manipulation of TH signaling (and other candidate pathways) modulates or rescues TKI-induced transcriptomic alterations in vitro. We hypothesize that the modulation of signaling pathways that overlap with those affected by TKIs - particularly TH signaling - can mitigate or rescue CRF-related TKI-induced transcriptome alterations. We will test whether manipulation of TH signaling (TH levels, transporters, deiodinases and receptors) and other relevant pathways identified in Aim 1 modulates or rescues TKI-induced changes. We will validate TKI-induced transcriptional changes in established in vitro neural cell model (i.e. SH-SY5Y cells and iPSC-derived human neurons), and select relevant gene and protein expression changes as readouts for rescue experiments. This analysis will provide biological evidence for the overlap between TKI-induced alterations and key signaling pathways in the context of CRF – including TH signaling, and identify candidate targets to mitigate or reverse TKI-induced adverse effects. Aim 3 Determine whether TH supplementation can reverse TKI-induced transcriptome alterations in vivo. We hypothesize that impaired D2 activity, by reducing brain T3 availability and impinging on TH-dependent regulatory networks, represents a key determinant of TKI-induced CRF. To test this hypothesis, TKI-treated C57BL/6 mice will receive TH to restore brain T3 levels. Mice will be treated with clinically appropriate doses and schedules of TKIs, with or without TH supplementation, and transcriptomic changes in the cortex, hippocampus, and cerebellum will be compared with untreated controls and mice treated with TH alone. We expect TH supplementation to rescue at least in part the TKI-induced transcriptional alterations, particularly those linked to CRF.

	These experiments will set the stage for subsequent translational studies in humans.
Recent bibliography	Intracellular inactivation of thyroid hormone is a survival mechanism for muscle stem cell proliferation and lineage progression. CELL METAB 2014 Dec; 20: 1038 Reciprocal interplay between thyroid hormone and microRNA-21 regulates hedgehog pathway-driven skin tumorigenesis. J CLIN INVEST 2016 Jun; 126: 2308 Type 2 Deiodinase in Cancer-Associated Fibroblasts is Required to Sustain Growth of Poorly and Undifferentiated Thyroid Cancer. THYROID 2026 Jan; 36: 71 The unique signature of tyrosine kinase inhibitor-induced hypothyroidism. LANCET DIABETES ENDO 2025 Sep; 13: 803 Type 2 deiodinase-dependent surge in thyroid hormone controls muscle stem cell quiescence and self-renewal. J CLIN INVEST 2026 May; 136:
Group composition	10 members: 1 Associate Professor in Endocrinology, 1 Assistent Professor in Endocrinology, 1 Post-doc fellow, 2 PhD students, 5 fellows (students)
Institutional page link	www.ceinge.unina.it