

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Enzo Tramontano

eRA COMMONS USER NAME (credential, e.g., agency login): ETRAMONTANO

POSITION TITLE: Professor of Microbiology and Virology, Chair of the Department of Life and Environmental Sciences

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Cagliari, Italy	MS	03/1990	Biology
Yale University Medical School, USA	Visiting Research Scientist	10/1992	Virology
University of Cagliari, Italy	Fellowship by Istituto Superiore di Sanità (Italian NIH)	10/1994	Virology
Sardinian Antiviral Research Consortium	Senior Scientist	10/1995	Virology
Yale University Medical School, USA	Visiting Research Scientist	10/1997	Virology

A. Personal Statement

I am the Chair of the Department of Life and Environmental Science of the University of Cagliari since 2021 (Italy) and Vice-President of the Italian Society for Virology (SIV-ISV) since 2022. I am a virologist mostly focused on the development of antiviral drugs and the study of endogenous retroviruses. More in detail, my research activities focus on i) antiviral drug discovery using both biochemical and cellular techniques to evaluate the ability of small molecules to block the enzymatic function of viral enzymes and to inhibit viral replication; iii) identification and characterization of retroviral sequences stably integrated into human genomes and definition of their transcriptome to explore their physiological and pathological role; iii) understanding the viral impact on the host cell and in particular on the pathways involved in the innate immunity viral evasion and cellular modifications also to exploit these molecular determinants as drug targets;.

In my carrier I mostly focused on retroviruses, filoviruses such as Ebola virus, coronaviruses and flaviviruses. I have served as Dean of the Faculty of Biology and Pharmacy (2015-2021) and Director of the PD program in Life and Environmental Science (2013-2019). Together with USA and European colleagues I organized seven editions of a summer school entitled "Innovative approaches for the identification of antiviral agents"

<https://sites.unica.it/iaaass/>. I also have been organizing officer for seven National meetings of the Italian Society for Virology and one for the Italian Society of General Microbiology. I have served as project reviewers for a number of international grant agencies and a panel member for the research grant evaluation for the Swedish Research Council. I am member of Editorial Board of Viruses, Section board for "Viral Immunology, Vaccines, and Antivirals". I have published more than 200 papers, with an H index of 45, and obtained 5 patents.

Ongoing and recently completed projects in which I was involved that I would like to highlight include:

- Co-Work Package Coordinator and Unit Coordinator of the multimillion PNRR PE13 MUR project entitled “INF-ACT, One Health Basic and Translational Research Actions addressing Unmet Needs on Emerging Infectious Diseases” (2022-2025)
- Unit coordinator of the EU H2020 grant entitled “Antiviral therapeutics for rapid response against pandemic infectious Diseases (Avithrapid)” (2023-2028)
- Scientific responsible of a Sardinian regional government grant to implement research infrastructures entitled “Vir-unica” (2022-2024)
- Unit responsible of the EU H2020 grant entitled “EXaSCale smArt pLatform Against paThogEns for Corona Virus (EXSCALATE4CoV)” (2020-2022)

B. Positions, Scientific Appointments, and Honors

2022-today	Vice-President of the “Società italiana di Virologia – Italian Society for Virology (SIV-ISV)”
2021-today	Director of the Department of Life and Environmental Sciences of the University of Cagliari
2017-2022	Member of the Executive Council of the “Società italiana di Virologia – Italian Society for Virology (SIV-ISV)”
2015-today	Full Professor of Microbiology at the Department of Life and Environmental Sciences of the University of Cagliari
2015-2021	Dean of the Faculty of Biology and Pharmacy of the University of Cagliari
2013-2019	Director of the PhD School in “Life, Environmental and Drug Sciences” of the University of Cagliari
2014-2017	Member of the Executive Council of the “Italian Society of General Microbiology and Microbial Biotechnologies” for the Virology division.
2014	Award for excellent International Research Project appointed by the Regione Autonoma della Sardegna assigned within the research premium system relative to the art. 13, of the Regional Law n.7/1007.
2013	Award for excellent National Research Project appointed by the Regione Autonoma della Sardegna assigned within the research premium system relative to the art. 13, of the Regional Law n.7/1007.
2012-2015	Vice-Director of the Department of Life and Environmental Sciences of the University of Cagliari
2006-2015	Associate Professor of General Microbiology at the Faculty of Sciences at the University of Cagliari
2001-2006	Assistant Professor of the Faculty of Sciences at the University of Cagliari
1998-2000	Research Associate at the Department of Experimental Biology of the University of Cagliari

C. Contributions to Science

1. My early publications were dedicated to the identification of novel anti-HIV agents targeted to reverse transcriptase (RT) and integrase (IN). In particular, I described the mode of action of Nevirapine. In addition I participated in the selection of the first HIV-1 drug resistant HIV obtained in cell-culture.

- Tramontano E.** and Cheng Y.C. HIV-1 reverse transcriptase inhibition by a dipyrindodiazepinone derivative: BI-RG-587. *Biochem. Pharmacol.* 43, 1371-1376 (1992).
- Mellors J.W., Dutschman G.E., Im G.-J., **Tramontano E.**, Winkler S.R., Cheng Y.-C. In vitro selection and molecular characterization of human immunodeficiency virus-1 resistant to non-nucleoside inhibitors of Reverse Transcriptase. *Mol. Pharmacol.* 41, 446-451 (1992).
- Mai A., Artico M., Sbardella G., Massa S., Loi A.G., **Tramontano E.**, Scano P. and La Colla P. Synthesis and anti-HIV-1 activity of thio analogues of DABOs (dihydroalkoxybenzylloxypyrimidines). *J. Med. Chem.* 38: 3258-3263 (1995).
- Artico M., Di Santo R., Costi R., Novellino E., Greco G., Massa S., **Tramontano E.**, Marongiu ME., Putzolu M. and La Colla P., Geometrically and conformationally restrained cinnamoyl compounds as inhibitors of HIV-1 integrase: synthesis, biological evaluation and molecular modeling. *J. Med. Chem.* 41: 3948-3960, (1998).

- e. Mai A., Artico M., Sbardella G., Massa S., Novellino E., Greco G., Loi A.G., **Tramontano E.**, Marongiu M.E. and La Colla P. 5-alkyl-2-(alkylthio)-6-(2,6-dihalophenyl-methyl)-3,4-dihydropyrimidin-4(3H)-ones: novel potent and selective dihydro-alkoxy-benzyl-oxopyrimidine derivatives J. Med. Chem. 42: 619-627, (1999).
- f. Richetta C, Subra F, Malet I, Leh H, Charpentier C, Corona A, Collin G, Descamps D, Deprez E, Parissi V, Calvez V, **Tramontano E**, Marcelin AG, Delelis O. Mutations in the 3'-PPT Lead to HIV-1 Replication without Integration. J Virol. 27, e0067622, (2022) doi: 10.1128/jvi.00676-22.

2. I kept working on anti-HIV drug development focusing on the RT-associated Ribonuclease H activity whose active site shares similarities with the HIV-1 IN site, describing a number of novel viral inhibitors.

- a. **Tramontano E.**, Esposito F., Badas R., Di Santo R., Costi R. and La Colla P. 6-[1-(4-Fluorophenyl)methyl-1H-pyrrol-2-yl]-2,4-dioxo-5-hexenoic acid ethyl ester a novel diketo acid derivative which selectively inhibits the HIV-1 viral replication in cell culture and the ribonuclease H activity in vitro. Antiv. Research 65: 117-124, (2005).
- b. Distinto S., Esposito F., Kirchmair J., Cardia MC., Gaspari M., Maccioni E., Alcaro S., Markt P., Wolber G., Zinzula L., **Tramontano E.** Identification of HIV-1 reverse transcriptase dual inhibitors by a combined shape-, 2D-fingerprint- and pharmacophore-based virtual screening approach Eur. J. Med. Chem. 50, 1-14 (2012)
- c. Costi R., Métifiot M., Esposito F., Cuzzucoli Crucitti G., Pescatori L., Messori A., Scipione L., Tortorella S., Zinzula L., Marchand C., Pommier Y., **Tramontano E.**, Di Santo R. 6-(1-Benzyl-1H-pyrrol-2-yl)-2,4-dioxo-5-hexenoic Acids as Dual Inhibitors of recombinant HIV-1 Integrase and Ribonuclease H, Synthesized by a Parallel Synthesis Approach. J Med Chem. 56, 8588- 8598 (2013)
- d. Corona A, Schneider A, Schweimer K, Rösch P, Wöhrl BM, **Tramontano E.** Inhibition of foamy virus reverse transcriptase by human immunodeficiency virus type 1 ribonuclease H inhibitors. (2014) Antim. Agents Chemother. 58, 4086-4093 (2014).
- e. Meleddu R, Distinto S, Corona A, Bianco G, Cannas V, Esposito F, Artese A, Alcaro S, Matyus P, Bogdan D, Cottiglia F, **Tramontano E.**, Maccioni E. 3Z)-3-(2-[4-(aryl)-1,3-thiazol-2-yl]hydrazin-1-ylidene)-2,3-dihydro-1H-indol-2-one derivatives as dual inhibitors of HIV-1 reverse transcriptase. Eur J Med Chem. 2015 93C: 452-460 (2015) doi: 10.1016/j.ejmech.2015.02.032.
- f. Cuzzucoli Crucitti G, Métifiot M, Pescatori L, Messori A, Madia VN, Pupo G, Saccoliti F, Scipione L, Tortorella S, Esposito F, Corona A, Cadeddu M, Marchand C, Pommier Y, **Tramontano E.**, Costi R, Di Santo R. Structure-Activity Relationship of Pyrrolyl Diketo Acid Derivatives as Dual Inhibitors of HIV-1 Integrase and Reverse Transcriptase Ribonuclease H Domain. J Med Chem. 58: 1915-28 (2015) doi: 10.1021/jm501799k.
- g. Corona A, Di Leva FS, Thierry S, Pescatori L, Cuzzucoli Crucitti G, Subra F, Delelis O, Esposito F, Rigogliuso G, Costi R, Cosconati S, Novellino E, Di Santo R, **Tramontano E.** Identification of highly conserved residues involved in the inhibition of the HIV-1 ribonuclease H function by diketoacid derivatives. Antimicrob Agents Chemother. 58: 6101-6110 (2014).
- h. Corona A, di Leva FS, Rigogliuso G, Pescatori L, Madia VN, Subra F, Delelis O, Esposito F, Cadeddu M, Costi R, Cosconati S, Novellino E, di Santo R, **Tramontano E.** New insights into the interaction between pyrrolyl diketoacids and HIV-1 integrase active site and comparison with RNase H. Antiviral Res. 134, 236-243. (2016) doi: 10.1016/j.antiviral.2016.09.008.

3. I then explored the interplay between the innate immune response activation and a number of viral proteins, mostly from Ebola virus and Zika Virus, also exploiting them as drug targets for drug development. To this purpose my lab has established both cellular and biochemical methods and applied them to drug discovery.

- a. Cannas V, Daino GL, Corona A, Esposito F and **Tramontano E.** A luciferase reporter gene assay to measure Ebola Virus viral protein 35-associated inhibition of double-stranded RNA-stimulated, retinoic acid-inducible gene 1-mediated induction of interferon β J. Infect. Disease 212 Suppl 2:S277-81 (2015). doi: 10.1093/infdis/jiv214.
- b. Le Sage V, Cinti A, McCarthy S, Amorim R, Rao S, Daino GL, **Tramontano E.**, Branch DR, Mouland AJ. Ebola virus VP35 blocks stress granule assembly. Virology 502, 73-83 (2017).
- c. Fanunza E, Frau A, Sgarbanti M, Orsatti R, Corona A, **Tramontano E.** Development and validation of a novel dual luciferase reporter gene assay to quantify ebola virus VP24 inhibition of IFN signaling. Viruses 10, 10 (2018) doi: 10.3390/v10020098

- d. Daino GL, Frau A, Sanna C, Rigano D, Distinto S, Madau V, Esposito E, Fanunza E, Bianco G, Taglialatela-Scafati O, Zinzula L, Maccioni E, Corona A, **Tramontano E** Identification of Myricetin as Ebola virus VP35-dsRNA interaction inhibitor through a novel fluorescence-based assay. *Biochemistry* 57: 6367-6378 (2018) doi: 10.1021/acs.biochem.8b00892
- e. Fanunza E, Iampietro M, Distinto S, Corona A, Quartu M, Maccioni E, Horvat B, **Tramontano E**. Quercetin blocks Ebola Virus infection by counteracting the VP24 Interferon inhibitory function. *Antimicrob. Agents Chemother* 64(7), e00530-20 (2020) doi: 10.1128/AAC.00530-20
- f. Fanunza E, Carletti F, Quartu M, Grandi N, Ermellino L, Milia J, Corona A, Capobianchi MR, Ippolito G and **Tramontano E**. Zika virus NS2A inhibits interferon signaling by degradation of STAT1 and STAT2. *Virulence* 12: 1580–1596, (2021) doi: 10.1080/21505594.2021.1935613
- g. Fanunza E, Grandi N, Quartu M, Carletti F, Ermellino L, Milia J, Corona A, Capobianchi MR, Ippolito G, **Tramontano E** INM1 Zika Virus NS4B Antagonizes the Interferon Signaling by Suppressing STAT1 Phosphorylation. *Viruses* 13: 2448 (2021) doi: <https://doi.org/10.3390/v13122448>
- h. Corona A, Strayer D, Distinto S, Daino GL, Paulis A, **Tramontano E**, Mitchell WM. Ebola virus disease: In vivo protection provided by the PAMP restricted TLR3 agonist rintatolimod and its mechanism of action. *Antiviral Research* 212: 105554 (2023) doi: 10.1016/j.antiviral.2023.105554

4. A more recent line of research has dealt with questions regarding the functional and pathological role of the human endogenous retroviruses (HERVs). To this aim we have mapped the > 3000 most complete HERVs, we have classified a number of HERV families and we have developed a specific pipeline to analyze their transcriptome.

- a. Vargiu L, Rodriguez-Tomé P, Sperber GO, Cadeddu M, Grandi N, Blikstad V, **Tramontano E**, Blomberg J. Classification and characterization of human endogenous retroviruses; mosaic forms are common. *Retrovirology* 13(1):7, (2016). doi: 10.1186/s12977-015-0232-y.
- b. Grandi N, Cadeddu M, Blomberg J, **Tramontano E** Contribution of type W human endogenous retroviruses to the human genome: characterization of HERV-W proviral insertions and processed pseudogenes *Retrovirology* 13 (1), 67 (2016) doi: 10.1186/s12977-016-0301-x
- c. Grandi N. and **Tramontano E**. Type W Human Endogenous Retroviruses (HERV-W) proviral integrations and their mobilization by L1 machinery: contribution to the human transcriptome and impact on the host physio-pathology. *Viruses* 2017, 9, 162; doi: 10.3390/v9070162
- d. Pisano MP, Grandi N, Cadeddu M, Blomberg J, **Tramontano E** Comprehensive characterization of the HERV-K(HML-6): overview of their structure, phylogeny and contribution to the human genome. *J. Virol* 93: 1-19 (2019) doi: 10.1128/JVI.00110-19
- e. Pisano MP, Tabone O, Bodinier M, Grandi N, Textoris J, Mallet F, **Tramontano E** RNA-seq transcriptome analysis reveals LTR-retrotransposons modulation in Human Peripheral Blood Mononuclear Cells (PBMCs) after in vivo Lipopolysaccharides (LPS) injection. *J Virol* 20, 94 e00587-20 (2020) doi: 10.1128/JVI.00587-20
- f. Díaz-Carballo D, Sahitya Saka S, Acikelli AH, Homp E, Erwes J, Demmig R, Klein J, Schröer K, Malak, S D'Souza F, Noa-Bolaño A, Menze S, Pano E Andrioff S, Teipel M, Dammann P, Klein D, Nasreen A, Tannapfel A, Grandi N, **Tramontano E**, Ochsenfarth C, Dirk Strumberg D. Enhanced antitumoral activity of TLR7 agonists via activation of human endogenous retroviruses by HDAC inhibitors. *Comm Biol* 4: 276 (2021) doi: 10.1038/s42003-021-01800-3
- g. Grandi N, Erbi MC, Scognamiglio S, **Tramontano E**. Human Endogenous Retrovirus (HERV) Transcriptome Is Dynamically Modulated during SARS-CoV-2 Infection and Allows Discrimination of COVID-19 Clinical Stages. *Microbiology spectrum* 11, 1-26 (2023) doi: 10.1128/spectrum.02516-22

5. The most recently open line of research has been focused on the identification of novel anti-coronavirus agents. My focused was mainly on SARS-CoV-2 main protease and helicase.

- a. Kuzikov M, Costanzi E, Reinshagen J, Esposito F, Vangeel L, Markus Wolf M, Ellinger B, Claussen C, Geisslinger G, Corona A, Iaconis D, Talarico C, Manelfi C, Cannalire R, Rossetti G, Gossen J, Albani S, Musiani F, Herzog K, Ye Y, Giabbai B, Demitri N, Jochmans D, De Jonghe S, Rymanants J, Summa V, **Tramontano E**, Beccari AR, Leyssen P, Storici P, Neyts J, Gribbon P, Zaliani A Identification of inhibitors of SARS-CoV-2 3CL-Pro enzymatic activity using a small molecule in-vitro repurposing screen. *ACS Pharm Transl. Sci* – 4, 1096-1110 (2021) doi: 10.1021/acspstsci.0c00216
- b. Costanzi E, Kuzikov M, Esposito F, Albani S, Demitri N, Giabbai B, Camasta M, **Tramontano E**, Rossetti G, Zaliani A, Storici P. Structural and Biochemical Analysis of the Dual Inhibition of MG-132 against SARS-

CoV-2 Main Protease (Mpro/3CLpro) and Human Cathepsin-L. International Journal of Molecular Sciences, 2021, 22(21), 11779 doi: 10.3390/ijms222111779

- c. Zaliani A, Vangeel L, Reinshagen J, Iaconis D, Kuzikov M, Keminer O, Wolf M, Ellinger B, Esposito F, Corona A, **Tramontano E**, Manelfi C, Herzog K, Jochmans D, De Jonghe S, Chiu W, Francken T, Schepers J, Collard C, Abbasi K, Claussen C, Summa V, Beccari AR, Neyts J, Gribbon P, Leyssen P. Cytopathic SARS-CoV-2 screening on Vero-E6 cells in a large-scale repurposing effort. Sci Data 9(1): 405. (2022) doi: 10.1038/s41597-022-01532-x.
- d. Pelliccia S, Cerchia C, Esposito F, Cannalire R, Corona A, Costanzi E, Kuzikov M, Gribbon P, Zaliani A, Brindisi M, Storici P, **Tramontano E**, Summa V Easy Access to α -Ketoamides as SARS-CoV-2 and MERS Mpro Inhibitors via the PADAM Oxidation Route Eur. J. Med. Chem. 244: 114853 (2022) doi: 10.1016/j.ejmech.2022.114853
- e. Corona A, Wycisk K, Talarico C, Manelfi C, Milia J, Cannalire R, Esposito F, Gribbon P, Zaliani A, Iaconis D, Beccari AR, Summa V, Nowotny M, **Tramontano E**. Natural compounds inhibit SARS-CoV-2 nsp13 unwinding and ATPase enzyme activities ACS Pharm Transl. Sci 5: 226-239 (2022) doi: <https://doi.org/10.1021/acsptsci.1c00253>
- f. Stefanelli I, Corona A, Cerchia C, Cassese E, Improta S, Costanzi E, Pelliccia S, Morasso S, Esposito F, Paulis A, Scognamiglio S, Di Leva FS, Storici P, Brindisi M, **Tramontano E**, Cannalire R, Summa V .Broad-spectrum coronavirus 3C-like protease peptidomimetic inhibitors effectively block SARS-CoV-2 replication in cells: Design, synthesis, biological evaluation, and X-ray structure determination. Eur J Med Chem 253, 115311 (2023). doi: 10.1016/j.ejmech.2023.115311
- g. Biolatti M, Blangetti M, Baggieri M, Marchi A, Gioacchini S, Bajetto G, Arnodo D, Bucci P, Fioravanti R, Kojouri M, Bersani M, D'Arrigo G, Siragusa L, Ghinato S, De Andrea M, Gugliesi F, Albano C, Pasquero S, Visentin I, D'Ugo E, Esposito F, Malune P, **Tramontano E**, Prandi C, Spyraakis F; Magurano F, Dell'Oste V Strigolactones as broad-spectrum antivirals against β -coronaviruses through targeting the main protease Mpro. ACS Inf Dis 9: 1310-1318 (2023) doi: 10.1021/acsinfecdis.3c00219
- h. Corona A, Madia VN, De Santis R, Manelfi C, Emmolo R, Ialongo D, Patacchini E, Messore A, Amatore D, Faggioni G, Artico M, Iaconis D, Talarico C, Di Santo R, Lista F, Costi R, **Tramontano E**. Diketo acid inhibitors of nsp13 of SARS-CoV-2 block viral replication. Antiviral Research 217: 105697 (2023) doi: 10.1016/j.antiviral.2023.105697
- i. Kuzikov M, Reinshagen J, Wycisk K, Corona A, Esposito F, Malune P, Manelfi C, Iaconis D, Beccari A, **Tramontano E**, Nowotny M, Windshügel B, Gribbon P, Zaliani A. Drug repurposing screen to identify inhibitors of the RNA polymerase (nsp12) and helicase (nsp13) from SARS-CoV-2 replication and transcription complex. Virus Research 343 (2024) 199356 doi: 10.1016/j.virusres.2024.199356