LUIGI FRATI, M.D.

Full Professor of General Pathology/Molecular medicine [1980- 2012]
Dean of the 1st Faculty of Medicine and Surgery [1990-2009]
Rector of the University of Roma "La Sapienza" [2008-2014]

CURRICULUM VITAE

Name	Luigi FRATI, MD
Birth	Siena, Italy, April 10, 1943
Fiscal Code-Italy	FRT LGU 43D10 I726X
Nationality	Italian
Marital Status	Married, 2 children
Languages	Italian, English, French
Employment	Full Professor of Med/04 General Pathology-Molecular Medicine, Faculty of Medicine, University of Roma *La Sapienza*; head of Division of Oncology, Policlinico Umberto I
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A. Education and Training

1960/61	H*igh school degree*, Liceo-Ginnasio Vincenzo Monti, Cesena
1961/67	*Student, Medicine and Surgery, 6 yrs Course*, Faculty of Medicine, Catholic University, Policlinico Gemelli, Roma
1961/67	S*tudent internship on biochemistry and neurobiology*, Lab. of Biochemistry and Neurobiology, National Research Council-Health Institute, and Istitute of Chemistry, Catholic University, Roma
1964, 1965	*Summer student*, Washington University, St. Louis, Mo, and Wellcome Laboratories, London
july 15 1967	*Graduated cum laude* [experimental thesis on the *granulocytosis-inducing factor*, presently G-CSF, isolated by L.F. et al.: Biochim Biophys Acta 1965;111:344]
1970-71	*Clinical Endocrinology Branch*, NIAMMD, NIH, Bethesda, Md, USA, visiting scientist
1970	*Specialty degree on Endocrinology*, University of Perugia
1973	*Specialty degree on Laboratory Medicine*, University of Ferrara
1982	*Specialty degree on Oncology*, University of Roma *La Sapienza*

B. Academic Positions

1967-1980	A*cting assistant Professor of General Pathology*, University of Perugia
1970-71	*Visiting scientist*, Clinical Endocrinology Branch, NIAMD, NIH, Bethesda, Md., USA
1972-1980	*Acting Professor of General Pathology*, Faculty of Sciences, University of Perugia; Faculties of Pharmacy and of Medicine and Surgery, University of Roma *La Sapienza*
1980-2012	*Full Professor of General Pathology* [from 1997 of *Molecular Medicine*], Faculty of Medicine and Surgery, University of Roma *La Sapienza*; *Head of the Division of Oncology*, University Hospital-Policlinico Umberto I, Viale Regina Elena 324, Roma
2014-	*Emeritus Professor* of *Molecular medicine*, University of Roma *La Sapienza*

C. National-International Academic and Scientific Societies-Institutions	
1991-2015	Accademia Nazionale di Medicina, Roma, membership
1997-	Federation of the European Ntl Academies of Medicine, Bruxelles, [2005-10, member of the Board; 2007-08, President; 2009- President emeritus and permanent member of the Board for scientific affairs]
1990-	American Association for Cancer Research, corresponding member # 6582
--------	International Association for Research on Epstein-Barr, corresponding member

D. Public National-International Offices	
D1. Public National Offices	
1980-1998	*National Universities Council*, Italian Minister of the University and Research, *member* (*Vice-President*, 1987-1990)
1984-1994	*National Research Council*, Research Ntl Programme on Oncology, Molecular Biology Programme, Director
1988-1992	*Institute of Biomedical Technologies*, National Research Council, Roma, *Director*
1988-1998	*Natl Council on Science and Technology*, Italian Minister University and Research, *member*
1990-1997	*National Bioethics Committee*, Roma, *member*
1993-1994	*National Drug Agency*, Ministry of Health, Roma, *member*
1994-1997	*Health National Council*, Ministry of Health, Roma, *President*
D2. Public International Offices	
1994-1998	UE, EMA-*European Medicine Agency*, Bruxelles and London, *member of the board*
1997-	UE, Federation of the European National Academies of Medicine, Bruxelles, member of the board, 2002-2004 President, Emeritus President and permanent member of the Board for scientific affairs

E. University Offices; National Research Agencies/Institutions	
1984-1990	Department of Experimental Medicine, University of Roma *La Sapienza*, Director
1983-1995	Natl Research Council-CNR, National research program on Oncology, programme on Molecular Oncology, Director
1983-2014	University of Roma *La Sapienza*, member of the administrative council and of the Senate
1989-2004	CNR-Ntl Research Council, Institute of Biotechnology, Roma, Director
1990-2010	University of Roma *La Sapienza*, Faculty of Medicine and Surgery, Dean [2003-2008 President of the Ntl. Council of the Deans]
1993-	Basic and Clinical Biomedical Research Institute-IRCCS Neuromed, Pozzilli-IS, Scientific Director
2004-2014	University of Roma *La Sapienza* Rectorate [2004-2008 vice-Rector; 2008-14 Rector]
2015	Italian Pasteur Institute-Cenci Bolognetti Foundation, Roma, President

F. Books - Journals [editorial board]

International Books	Aaronson S, Frati L, Verna R, *Genetic and phenotypic markers of Tumors*, Plenum Press, NY, 1984 Bolis L, Verna R, Frati L, *Peptide hormones, biomembranes and cell growth*, Plenum Press, NY, 1984 Frati L, Aaronson S, *Molecular pathology of gene expression*, Raven Press, NY, 1989 Verna L, Blumenthal R, Frati L, *Bioengineered molecules: basic and clinical aspects.* Raven Press, 1989 Forni G, Foà R, Santoni A, Frati L, *Citokine-induced tumor immunogenicity [from exogenous moleculaes to gene therapy*, Academic Press, NY, 1994

Editorial board	Oncology Research [editorial board]
Editor	J Cellular Molecular Medicine [editorial board]

G. Fields of Research [*>600 Med-line indexed publications; >2000 I.F; > 12.500 citations; 2015 Hirsch index 56 ISI-web of knowledge*,]

G1. *Growth factors and Regenerative Medicine*

The main field of research is related to the molecular-cellular effects of growth factors and regenerative medicine.

Granulocytosis-inducing factor [now **G-CSF**] is isolated in 1965 [BBA 1965; 111:344-46] and demonstrated to be able to stimulate the granulocytes' bone marrow reservoir as well as the growth of progenitors and cardiac stem cells [i.e. cardiomyocytes: Circ Res 2004;95:911-21]

A continous field of research has been done on **Epidermal Growth Factor.** Labelled **EGF**-*epidermal growth factor* is found to be bound to many tissues, of which with higher affinity to corneal epithelium [Eur J Biochem 1992; 27:225-30], from which the receptor is isolated [Life Sci 1976; 18:905-11] and used for EGF-competitive radiorecep-tor assay. It is found a non-random distribution of the receptor on the plasma membranes [Exp Cell Res 1988; 175:326-33] and a process of internalization as EGF-EGF*r* complex , which is upregulated in both normal and tumor cells only if the receptor is not mutated [Cancer Res 1991; 51:1294-99]. The studies on the internalization of the EGF*r* open the way to investigate the surface distribution and internalization of erbB-2 receptors [Exp Cell Res 1992; 202:274-80]. The down-regulation of native EGF*r* induced by estrogens promotes the differentiation of human sarcoma cells [J Cell Physiol 2009; 220:35-44]

The **KGF**-*keratinocyte growth factor* is differentiated from EGF family for their coupling with the specific recep-tors [J Cell Physiol 1990; 144:326-32; J Cell Physiol 2004; 200:31-44] in cultured keratinocytes [Cell Growth Differ 1997; 8:989-97], with a receptor-mediated endocytosis [J Cell Sci 1998; 111:3517-27] and a receptor up-modulation [Cell Growth Differ 2000; 11:607-14]. UVB rays induce the internalization of KGF*r* [Oncogene 2003; 22:2422-31] trough endocytic pathways [FASEB J 2006; 20:395-7] and AKT and MAPK signaling [J Cell Physiol 2007; 212:633-42].

Growth Factors are used in **regenerative medicine**: i. of **corneal epithelium**, induced by EGF [Albrecht von Graefes Arch Klin Exp Ophthalmol 1979;7:159-165]; ii. of autologous *in vitro* cultured **vaginal tissue**, which is useful for vaginoplasty, e.g. in patients with von-Rotansky-Kuster-hauser syndrome [Hum Reprod 2007;22:2025-8]; iii. of adult **cardiac stem cells** taken from human and murine heart and expanded *in vitro* to generate beating cardiospheres useful to restore heart function [Circ Res 2004;95:911-21]; iv. of **hair stem cells** from transected follicles [Dermatol Surg 2009]

G2. *Molecular-Viral oncogenesis and Oncogenes*

The **EBV** virus-producing cells of nasopharyngeal carcinomas [J Exp Pathol 1987; 3:417-7] show the envelope glycoproteins on the inner nuclear membrane [J Virol 1989; 63:828-32]; the EBV

internalization and infectivity is blocked by selective PK-C inhibitors [Int J Cancer 1990; 45:490-93], whereas the BFRF1 gene of EBV ecodes a specific protein [J Virol 2000; 74:3235-44].

Cancers are associated with many **molecular defects**, i.e.the primitive breast cancer with the amplification of int-2, bcl-1, myc, erb-e etc.proto-oncogenes [Int J Cancer 1995; 61:1-6], the gastric cancer with mutations of coding mononucleotide repeats [Oncogene 1998; 16:2767-72]. In breast cancer subcellular localization of the BRCA1 gene product may be found in the mitotic cells [Genes Chromosomes Cancer 2002; 35:193-203; Ann Oncol 2006; 17:34-40], whereas genomic rearrangements of both BRCA 1 and BRCA2 have been found in breast and/or ovarian cancer [Breast Cancer Res Treat 2007;106:289-96; J Clin Oncol 2007; 25:2632-4], with DNA missense variants [J Clin Oncol 2008; 26:4212-4].

EGF*r* has been isolated first by our group from the corneal epithelium and used for a radioreceptor assay (Eur J Biochem, 1972; Exp Eye Res 1972; Life Sciences 1976). EGF*r* is wide expressed in tumor cells,also as truncated receptor or overexpressed and amplified in the various molecular forms [Exp Cell Res 2004;294:469-79; Mol Carcinog 2003;38:188-200]. On the other hand the ***Notch*-family** receptors are highly conserved in the species' evolution and structuraly related to the EGF*r*: thus, the role of *Notch* is studied in intrathymic T cell development [Int Immunol 1999;11:1017-25]; by generating Notch3 trasgenic mice, it was found that all mice [100%] develop T-cell leukemia/lymphoma [EMBO J 2000;19:3337-48]. Combined expression of pTalpha and Notch3 in T-cell leukemia identifies the requirement of preTCR for leukemia [Proc Natl Acad Sci USA 2002; 99:3788-93], so that it is demonstrated that Notch is a unifying target in T-cell acute lymphoblastic leukemia [Trends Mol Med 2003;9:30-5; EMBO Rep 2003; 4:1067-72; Oncogene 2005;24:992-1000; EMBO J 2006; 25:1000-8; EMBO J 2007; 26:1670-80; Int Immunol 2009; 21:727-43].

G3. *Modulation of Immune response and mechanism of action of the Biological response modifiers*

A neuromodulatory loop is mediated by growth factors, i.e. **NGF-***nerve growth factor* and IL-6 in thymic stromal cell cultures [Proc Natl Acad Sci 1992; 89:2867-71] and **EGF**, which enhances neuropoietic cytokine expression [J Cell Biol 1995; 130:183-92].

A series of studies is dedicated to **NK-***natural killer* cells and their mechanism of action in the immunosurveillance against tumor: their adhesion to laminin is triggered through CD16 or phorbol esters [J Exp Med 1992; 176:1251-7] with a NK long term activation triggered by CD44 [J Immunol 1994; 153:4399-407], which results in a modulation of β1-integrin expression [J Immunol 1994; 152:446-54] and protein tyrosine phosphorylation mediated by the interaction with fibronectin [J Immunol 1994; 154:3128-37; Eur J Immunol 1966; 26:2807-11]. CD94/NKG2-A inhibitory complex blocks CD16-triggered Syk and extracellular regulated kinase activation, leading to the cytotoxic functions of *hNK* cells [J Immunol 1999; 162:7181-8; Proc Natl Acad Sci USA 2001; 98:9611-6; J Biol Chem 2002; 277:36940-7].

G4. *Therapies in medical oncology*

Epithelial mucins are epitopes expresses by cancer cells, i.e. ovarian cancer [Eur J Cancer 1996; 32A:2155-63], useful to induce antitumor immunity by transfected human **dendritic cells** [Gene Ther 2000; 7:1458-66], generated in serum or serum-free media [J Immunother 2007; 30:567-76], combining chemotherapy, biological therapies and immunotherapy [Curr Cancer Drug Targets 2009; 9:541-65; N Engl J Med 2009; 360:2134-5].