

BIOGRAPHICAL SKETCH

| NAME | POSITION TITLE |
|-----------------------|----------------|
| Carlomagno, Francesca | Full Professor |

EDUCATION/TRAINING

| INSTITUTION AND LOCATION | DEGREE | MM/YY | FIELD OF STUDY |
|--|------------------|-----------|--------------------|
| Universita' degli studi di Napoli | Medicine. | 1993 | Molecular oncology |
| National Institutes of Health, Bethesda, MD, USA | Graduate Student | 1994 | Molecular oncology |
| Universita' degli studi di Napoli | PhD | 1998 | Molecular oncology |
| Cambridge University UK | Post doc. | 1997-1998 | Cancer Genetic |

A. Personal Statement

Francesca Carlomagno research group is interested in studying connections between iron availability and cell cycle control. In particular, they are investigating the control of iron release from ferritin, DNA replication origin activation and maintenance of genome stability by the transcriptional regulator NCOA4. By combining *in vitro* and *in vivo* study they are exploring the role of NCOA4 in responding to iron deprivation or DNA damage promoting cell cycle arrest and iron release from ferritin (ferritinophagy). In addition, in collaboration with prof. Massimo Santoro, the group aims at identifying RET and TRKs kinase inhibitors. RET and TRKs genes are frequently affected by oncogenic conversion in different types of human cancers. In the past they have identified several RET kinase inhibitors that have been tested in clinical trials. Among those, one, vandetanib, has been approved by FDA and EMA for treatment of metastatic or locally advanced medullary thyroid carcinoma. Currently, they are trying to identify new leads to develop novel therapies, with a special interest for RET/TRKs-driven human tumours such as lung and thyroid carcinomas or leukaemia.

B. Positions and Honors

Positions and Employment

- 1990-1993** **Ungraduate student** in prof Giancarlo Vecchio Laboratory, Dip. di Biologia e Patologia Cellulare e Molecolare, Facolta' di Medicina e Chirurgia and Centro per la Endocrinologia e l'Oncologia Sperimentale "G. Salvatore", Universita' di Napoli Federico II.
- 1992** **Summer Student** in Dr SA Aarosan laboratory, LCMB, NCI, NIH, Bethesda, Md, USA
- 28.7.1993** **Degree** in Medicine at Uniniversita' degli Studi di Napoli summa cum laude.
Thesis title: "Activation of RET gene in Thyroid Tumours"
- 1994** **Visiting Fellow** in Dr S. Tronick laboratories, LCMB, NCI, NIH, Bethesda, Md, USA
- 1994-1999** **PhD** in "Biologia e Patologia Cellulare e Molecolare"
Research Group: Laboratorio Prof. G. Vecchio, Dip. of Biologia e Patologia Cellulare e Molecolare, Facolta' di Medicina e Chirurgia e Centro di Studio per la Endocrinologia e l'Oncologia Sperimentale "G. Salvatore", Universita' di Napoli Federico II.
Thesis title: Effect of RET mutations found in human neoplastic and developmental diseases
- 1997- 1999** EC (European Community) **Fellow "Marie Curie"** in Prof. B.A.J. Ponder, Dept. of Pathology, University of Cambridge, UK.
- 1999- 2000** **Start Up Fellowship of Telethon Foundation** for Italian young researcher with at least two years experience abroad.

Host research group: laboratory of Prof. G. Vecchio, Dip. di Biologia e Patologia Cellulare e Molecolare, Facoltà di Medicina e Chirurgia and Centro di Studio per la Endocrinologia e l'Oncologia Sperimentale "G. Salvatore", Università di Napoli Federico II.

2001-2010 Permanent Position as **researcher** of Centro di Endocrinologia e Oncologia Sperimentale, CNR, c/o Dipartimento di Biologia e Patologia Cellulare e Molecolare, Università degli Studi di Napoli Federico II

2010-2018 Associate Professor of General Pathology at the Medical School, Dipartimento di Medicina Molecolare e Biotecnologie Mediche, Università degli Studi di Napoli Federico II

2019 up today Full Professor of General Pathology at the Medical School, Dipartimento di Medicina Molecolare e Biotecnologie Mediche, Università degli Studi di Napoli Federico II

Other Experience and Professional Memberships

-) Part of the executive committee of European Thyroid Association-Cancer Research Network since 2009
-) Part of the executive committee of Associazione Italiana Tiroide since 2008.
-) Associate Editor Thyroid Research journal since 2008
-) Scientific committee AIRC since 2019

Honors and Awards

May 2003 Winner of the “**Franco Tatò**” prize for Italian young researchers (under 35) in basic or clinical oncology given by Associazione Italiana per la Ricerca sul Cancro (AIRC) and by Società Italiana di Cancerologia (SIC)

June 2007 International award “**Gaetano Salvatore**” for physiopathology of the thyroid given by Accademia dei Lincei

Sept. 2011 International Award “**Harington-de Visscher**” for significant contribution to thyroid research given by European Thyroid Association.

C. Contributions to Science (selected from 90 scientific publications)

- 1. Study of MEN2 and Hirschsprung disease-associated mutations of RET gene and their effect on RET function and tumorigenesis. These studies helped in understanding how RET gain of function mutations associated to cancer and loss of function mutations associated to congenital megacolon where altering the activity of the receptor and its signalling.**

Carlomagno F, Melillo RM, Visconti R, Salvatore G, De Vita G, Lupoli G, Yu Y, Jing S, Vecchio G, Fusco A, Santoro M. GDNF differentially stimulates Ret mutants associated with the multiple endocrine neoplasia type 2 syndromes and Hirschsprung's disease. *Endocrinology (USA)* (1998) 139: 3613-9. ISSN: 0013-7227; doi: 10.1210/en.139.8.3613

Carlomagno F, Salvatore G, Cirafici AM, De Vita G, Melillo RM, de Franciscis V, Billaud M, Fusco A, Santoro M. The different RET activating capability of mutations of cysteine 620 or cysteine 634 correlates with the multiple endocrine neoplasia type 2 disease phenotype. *Cancer Res (USA)* (1997), 57: 391-5 ISSN: 0008-5472

Carlomagno F, De Vita G, Berlingieri MT, de Franciscis V, Melillo RM, Colantuoni V, Kraus MH, Di Fiore PP, Fusco A, Santoro M. Molecular heterogeneity of RET loss of function in Hirschsprung's disease. *EMBO J (England, UK)* (1996), 15: 2717-25 ISSN: 0261-4189

Carlomagno F, Salvatore D, Santoro M, de Franciscis V, Quadro L, Panariello L, Colantuoni V, Fusco A. Point mutation of the RET proto-oncogene in the TT human medullary thyroid carcinoma cell line. *Biochem Biophys Res Commun (USA)* (1995), 207: 1022-8. ISSN: 0006-291X; doi:10.1006/bbrc.1995.1287

Santoro M, Carlomagno F, Romano A, Bottaro DP, Dathan NA, Grieco M, Fusco A, Vecchio G, Matoskova B, Kraus MH, Di Fiore PP. Activation of RET as a dominant transforming gene by germline

mutations of MEN2A and MEN2B. *Science (USA)* (1995), 267: 381-3. ISSN: 0036-8075; doi: 10.1126/science.7824936

2. Identification of new targeted therapies for cancer treatment. In this field, the identification of particularly RET inhibitor vandetanib has been of crucial importance since this has been the first anti-RET compound to be approved in clinic for treatment of Medullary Thyroid Carcinoma. Other important findings have been the discovery of possible mechanism of resistance to anti-RET compounds via mutation of specific RET residues

Frett B*, Carlomagno F*, Moccia ML, Brescia A, Federico G, De Falco V, Admire B, Chen Z, Qi W, Santoro M, Li HY. (* co-first authors). Fragment-Based Discovery of a Dual pan-RET/VEGFR2 Kinase Inhibitor Optimized for Single-Agent Polypharmacology. *Angew Chem Int Ed Engl.* 2015 Jul 20;54(30):8717-21. doi: 10.1002/anie.201501104.

Alfano L, Guida T, Provitera L, Vecchio G, Billaud M, Santoro M, Carlomagno F. RET is a heat shock protein 90 (HSP90) client protein and is knocked down upon HSP90 pharmacological block. *J Clin Endocrinol Metab (USA)* (2010) 95: 3552-7. ISSN: 0021-972X; doi: 10.1210/jc.2009-2315

Guida T, Anaganti S, Provitera L, Gedrich R, Sullivan E, Wilhelm SM, Santoro M, Carlomagno F. Sorafenib inhibits imatinib-resistant KIT and platelet-derived growth factor receptor beta gatekeeper mutants. *Clin Cancer Res (USA)* (2007) 13: 3363-9. ISSN: 1078-0432; doi: 10.1158/1078-0432.CCR-06-2667

Carlomagno F, Anaganti S, Guida T, Salvatore G, Troncone G, Wilhelm SM, Santoro M. BAY 43-9006 inhibition of oncogenic RET mutants. *J Natl Cancer Inst (USA)* (2006), 98:326-34. ISSN: 0027-8874; doi:10.1093/jnci/djj069

Carlomagno F, Guida T, Anaganti S, Vecchio G, Fusco A, Ryan AJ, Billaud M, Santoro M. Disease associated mutations at valine 804 in the RET receptor tyrosine kinase confer resistance to selective kinase inhibitors. *Oncogene (England, UK)* (2004), 23: 6056-63. ISSN: 0950-9232; doi: 10.1038/sj.onc.1207810

Carlomagno F, Vitagliano D, Guida T, Ciardiello F, Tortora G, Vecchio G, Ryan AJ, Fontanini G, Fusco A, Santoro M. ZD6474, an orally available inhibitor of KDR tyrosine kinase activity, efficiently blocks oncogenic RET kinases. *Cancer Res (USA)* (2002), 62: 7284-90. ISSN: 0008-5472

Carlomagno F, Vitagliano D, Guida T, Napolitano M, Vecchio G, Fusco A, Gazit A, Levitzki A, Santoro M. The kinase inhibitor PP1 blocks tumorigenesis induced by RET oncogenes. *Cancer Res (USA)* (2002), 62: 1077-82 ISSN: 0008-5472

3. Study of the connections between iron homeostasis, DNA replication and DNA repair. This a completely novel field in which the specific role of NCOA4 protein, involved in controlling DNA replication and release of iron from ferritin in iron deprivation conditions, is being explored in correlation with diseases such anaemia, cancer and hemochromatosis.

Bellelli R, Federico G, Matte' A, Colecchia D, Iolascon A, Chiariello M, Santoro M, De Franceschi L, Carlomagno F. NCOA4 Deficiency Impairs Systemic Iron Homeostasis. *Cell Rep.* 2016 Jan 26;14(3):411-21. doi:10.1016/j.celrep.2015.12.065.

Bellelli R, Castellone MD, Guida T, Limongello R, Dathan NA, Merolla F, Cirafici AM, Affuso A, Masai H, Costanzo V, Grieco D, Fusco A, Santoro M, Carlomagno F. NCOA4 transcriptional

coactivator inhibits activation of DNA replication origins. *Mol Cell (USA)* (2014) 55: 123-37. ISSN: 1097-2765; doi: 10.1016/j.molcel.2014.04.031.

Guida T, Salvatore G, Faviana P, Giannini R, Garcia-Rostan G, Provitera L, Basolo F, Fusco A, Carlomagno F, Santoro M. Mitogenic effects of the up-regulation of minichromosome maintenance proteins in anaplastic thyroid carcinoma. *J Clin Endocrinol Metab (USA)* (2005), 90: 4703-9. ISSN: 0021-972X; doi:10.1210/jc.2004-2459

Carlomagno F, Burnet NJ, Turesson I, Nyman J, Peacock JH, Dunning AM, Ponder BAJ, Jackson SP. Comparison of DNA repair protein expression and activities between human fibroblast cell lines with different radiosensitivities. *Int J Cancer (Switzerland)* (2000), 85: 845-9. ISSN: 0020-7136; doi: 10.1002/(SICI)1097-0215(20000315)85:6<845