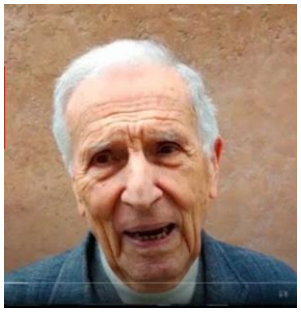

Vittorio Enrico Avvedimento, is professor Emeritus of General Pathology University "Federico II" Napoli, Dept of Molecular Medicine and Medical Biotechnology at the *Medical School*. He received his MD degree at the University of Napoli and completed the residency in Neurology at the *School of Neurology* of the same University. He was fellow in 1978-80 in the laboratory of Molecular Biology, at the *National Cancer Institute*, NIH, in Bethesda (USA). In 1987 he was awarded the *Eleanor Roosevelt Fellowship, American Cancer Society*. In 2002 he spent the year at the *Institute of Cancer Research*, Columbia University, as "*L. Schaffner*" Visiting Professor. 2009 *Scholar In residence* Columbia University.

He was coordinator of the PhD program in *Molecular Medicine and Medical Biotechnology* at the University "Federico II," Napoli from 2013 to 2019. 2003 -2012 he was the coordinator of the PhD Program Pathology and Molecular Pathophysiology, which was ranked in 2007 first among the 120 PhD programs of the University by an independent panel of reviewers.

Expertise : Cancer biology, Epigenetics, DNA methylation, Transcription, DNA damage, autoimmune diseases.

Research and Professional Experience

1978-1979	Fogarty Fellowship at the Laboratory of Molecular Biology, Sect. Gene Regulation, National Cancer Institute, National Institutes of Health, Bethesda, Md, USA
1980- 1981	Visiting Associate at Laboratory of Molecular Biology, National Cancer Institute, National Institutes of Health, Bethesda, Md, USA
1987-1988	American Cancer Society Fellow at the Institute of Cancer Res., Columbia University, New York, NY, USA
1990-1991	Visiting Scientist Institute of Cancer Research, Columbia University, New York

Honors and Awards

1977	*National Academy of Medicine* Award (US $ 1,000)
1988	*Eleanor Roosevelt-American Cancer Society Fello*w
1997-2000	Board of Directors *R. Ceppellini Advanced School of Immunology*
2001-2002	"*L.Schaffner" Visiting Professor* award, Columbia University Medical School, College of Physicians and Surgeons, New York, New York, USA.
2005 - 2008	Start Cup "Federico II" award Biotech (see web Winners 2005 and 2008 Start Cup Federico II).
2009	*Scholar in Residence* Italian Academy Advanced Studies, Columbia University, New York, USA
2010	*Faculty of 1000 Prime***,** Section Cell Biology- Cell Signalling
2009-2013	Member Scientific Board AIRC (Associazione Italiana Ricerca Cancro) . National Coordinator PRIN (Progetti di Rilevante Interesse Nazionale) **2001-2003-2006**- Local Coordinator PRIN **2008- 2017**. Member ASN- **2015**-2017

For specific information see the site
http://unina.academia.edu/EnricoVAvvedimento

2007-2022 Publications
VE Avvedimento
H=60

1. 1980-1986. The FIRST Cloning of two largest (1980-1986) mammalian genes: Collagen and Thyroglobulin genes. Mechanism of splicing.

i. Cloning and Structure of the first (prototypic) vertebrate Collagen gene

The structure of the first cloned collagen gene ((2) type I) indicated a common architectural motif: an exon unit of 54 (18 amino acids) corresponding to the helical domain of the protein. This finding was the first evidence for the evolutionary assembly of collagen genes by amplification of the 54 bp DNA segment. **Later, this unit turned out to be the common building block of all collagen genes in vertebrates.**

Yamada,Y., Avvedimento,V.E., Mudryj, M., Ohkubo,H.,Vogeli, G., Irani, M., Pastan,I. and De Crombrugghe B. **(1980)** *The collagen gene : evidence for its evolutionary assembly by amplification of a DNA segment containing an exon of 54 bp.* **Cell 22, 887-892.***

ii. Splicing of the collagen pre-mRNA: mechanism of splicing. The analysis of the primary transcript of collagen genes revealed that the exon-intron junctions showed a strong complementarity to U1 sRNA. At 46 b from the exon junction (3'site) there were overlapping sequences complementary to small U1 RNA. Pre-mRNAs in vivo containing these sequences partially spliced were for the first time detected. The region cat the 3'end of the intron orresponds to the lariat structure, that was defined 5 years later.

Avvedimento,V.E., Yamada,Y.,Vogeli,G., Maizel,J.V.Jr, Pastan,I. and De Crombrugghe, B. **(1980)** *Correlation between splicing sites within an intron and their sequence complementarity with U1 RNA.* **Cell 21, 689-696**.*

iii. Thyroglobulin Gene The rat thyroglobulin gene was completely cloned in the 1986 and it turned out to be 250 Kb long with introns ranging from 60 Kb to 150 bp. The structure of this gene revealed a composite architecture of the transcription unit and of the protein: The same structure of the rat gene was later found in the human and bovine genes.

Musti, A.M., Avvedimento,V.E., Polistina,C., Ursini,M.V., Obici, S., Nitsch, L., Cocozza,S. and Di Lauro , R. **(1986)** *The complete structure of rat thyroglobulin gene*. **Proc. Natl.Acad.Sci.USA 83,323-327.***

2. 1986-1996. **Ras impairs cAMP signaling (transcription and replication) to the nucleus. Ras impacts substantially the transmission of cAMP signals**. cAMP restrains the growth, RAS stimulates it. In many cell types AMP reduces growth and induces differentiation, while RAS induces signals that delocalize from membranes to the cytosol PKA anchor proteins and PKA. This leads to the inhibition cAMP-PKA signal transmission to the nucleus.

1. Avvedimento, V.E., Obici, S., Sanchez, M., Gallo,A., Musti,A.M. and Gottesman, M.E. (1989*) Reactivation of thyroglobulin gene expression by 5-Azacytidine in transformed thyroid cells*. **Cell 58, 1135-1142.***

2. Avvedimento,V.E., Musti,A.M., Ueffing,M., Obici,S., Gallo,A., Sanchez,M., De Brasi,D. and Gottesman , M.E. (1991) *Reversible inhibition of a thyroid specific transacting factor by Ras*. **Gen. Dev. 5, 22-28.**

3. Gallo, A., Benusiglio E., Bonapace, I.M., Feliciello, A., Cassano, S., Garbi, C., Musti, AM., Gottesman, M.E. and Avvedimento V.E. (1992) V-*RAS PKC dedifferentiate thyroid cells by downregulating nuclear cAMP dependent protein kinase A.* **Gen. Dev. 6,1621.***

4. Feliciello A, Giuliano P, Porcellini A, Garbi C, Obici S, Mele E, Angotti E, Grieco D, Amabile G, Cassano S, Li Y, Musti AM, Rubin CS, Gottesman ME, Avvedimento EV. *The v-Ki-Ras oncogene alters cAMP nuclear signaling by regulating the location and the expression of cAMP-dependent protein kinase IIbeta.* **J Biol Chem. 1996 Oct 11;271(41):25350-9.**

ii. cAMP-PKA control mitosis

Grieco D, Porcellini A, Avvedimento EV, Gottesman ME. (1996) *Requirement for cAMP-PKA pathway activation by M phase-promoting factor in the transition from mitosis to interphase.* **Science 1996;271(5256):1718-23***

3. 1996-2006. Ras genes control REDOX balance. Impact on human diseases: Pathogenesis and Somatic gene therapy of cardiovascular and autoimmune diseases (systemic sclerosis)

i. Ki and Ha Ras regulate redox signals in opposing fashion.

Ki and Ha Ras isoforms regulate the levels of reactive oxigen species in opposite fashion: Ha Ras stimulates NADPHoxidase and increases ROS, whereas Ki Ras induces mitochondrial SOD and decreases ROS.

Santillo, M., Mondola, P., Serù, R., Cassano, S., Ciullo, I., Tecce, Iacomino, G., Cuda, G, Paterno, Martignetti, V, Feliciello, A. and Avvedimento V.E. **(2001)** Opposing functions of Ki ha Ras genes in the regulation of redox signals. **Current Biology 11:614-619.**

ii. Inhibition of Ras *in vivo* blocks cell proliferation induced by vascular injury.

i. Lesions of the arterial wall in vivo are followed by proliferation of smooth muscle cells of the intima, which leads to the restenosis and lumen reduction. Local delivery of expression vectors coding for transdominant negative variants of Ras, inhibited efficiently the restenosis of the vessel. Pharmacological inhibition of Ha Ras in vivo attenuated the response to stress, since it reduced ROS and improved survival in heart and kidney subjected to ischemia-reperfusion.

1. Indolfi, C., Avvedimento, V.E., Di Lorenzo, E., Rapaciuolo, A., Feliciello, A., Giuliano, P., Mele, E., Condorelli, G.L. and Chiariello, M. **(1995)** *Inhibition of cellular Ras in vivo prevents neointimal proliferation in smooth muscle cells.* **Nature Medicine 1, 541-545. * (see comments and N&V in the same issue or in Nature 375, 433)**

2. C.Indolfi, E.V.Avvedimento, E.Di Lorenzo, G.Esposito, A.Rapacciuolo, P.Giuliano, Grieco, D., Cavuto, L., Stingone,A. and Chiariello, M. *Activation of cAMP-PKA signalling in vivo inhibits smooth muscle cell proliferation induced by vascular injury* **(1997) Nature Medicine 3, 775-779.**

3. Indolfi, C. , Chiariello, M. and Avvedimento, V.E. **(1996)** *Selective gene therapy of proliferative disorders.* **Nature Medicine 2, 634-635.**

iii. Functional amplification of Ha Ras in vivo: isolation of stimulating auto-antibodies to PDGFR in systemic sclerosis

1. Svegliati Baroni SS, Santillo M, Bevilacqua F, Lucchetti M , Spadoni T., Mancini, M., Fraticelli P., Sambo P, Funaro, A.,Kazlauskas, A., Avvedimento VE*, GabrielliA*.*corresponding authors Stimulatory autoantibodies to the PDGF receptor in systemic sclerosis **New Engl. J.Med (2006)** 354(25):2667-76.

2. A. Gabrielli, E.V.Avvedimento and T. Krieg.Scleroderma **N.Engl.J. Med. (2009) 360:1989-2003**

4. 2006- 2021 : Linking Epigenetics, Transcription with DNA damage and repair. Transcription driven by DNA oxidation: mechanism(s) and consequence(s)

i. DNA methylation marks DNA damage and homologous repair

1. Cuozzo C, Porcellini A, Angrisano T, Morano A, Lee B, Pardo AD, Messina S, Iuliano R, Fusco A, Santillo MR, Muller MT, Chiariotti L, Gottesman ME, Avvedimento EV. *DNA Damage, Homology-Directed Repair, and DNA Methylation.* **PLoS Genet. 2007** vol. 3, pp. 1144-1162

See comments http://www.nature.com/nrg/journal/v8/n7/full/nrg2156.html <http://www.nature.com/nrg/journal/v8/n7/full/nrg2156.html>

2. A. Morano, T. Angrisano, G. Russo, R. Landi, A. Pezone, S. Bartollino, C. Zuchegna, F. Babbio, M. Bonapace, B. Allen, M. T. Muller, L. Chiariotti, M.E. Gottesman, A.Porcellini and E.V. Avvedimento. *Targeted DNA methylation by homology-directed repair in mammalian cells . Transcription reshapes methylation on the repaired gene.* **Nucleic Acids Res. 2013: 1-18.**

3. Russo G, Landi R, Pezone A, Morano A, Zuchegna C, Romano A, Muller MT, Gottesman ME, Porcellini A, Avvedimento EV.DNA damage and Repair Modify DNAmethylation and Chromatin Domain of the Targeted Locus: Mechanism of allele methylation polymorphism .**Sci Rep. 2016 Sep 15;6:33222.**

ii. Transcription is driven by DNA oxidation

1. Perillo B, Ombra MN, Bertoni A, Cuozzo C, Sacchetti S, Sasso A, Chiariotti L, Malorni A, Abbondanza C, Avvedimento EV. *DNA oxidation as triggered by H3K9me2 demethylation drives estrogen-induced gene expression.* **Science, 2008 Jan 11**;319(5860):202-6

2. Pezone A, Taddei ML, Tramontano A, Dolcini J, Boffo FL, De Rosa M, Parri M, Stinziani S, Comito G, Porcellini A, Raugei G, Gackowski D, Zarakowska E, Olinski R, Gabrielli A, Chiarugi P, Avvedimento EV. *Targeted DNA oxidation by LSD1-SMAD2/3 primes TGF-β1/ EMT genes for activation or repression.* **Nucleic Acids Res. 2020 Sep** 18;48(16):8943-8958. doi:.

See comments Carl Nathan1,2 and Amy Cunningham-Bussel1, Beyond oxidative stress: an immunologist's guide to reactive oxygen species

NATURE REVIEWS | I350 | MAY 2013 | VOLUME 13 349-361.

See review: Yick W. Fong,1 Claudia Cattoglio,1 and Robert Tjian. The Intertwined Roles of Transcription and Repair Proteins. **Molecular Cell** , 2013, 52: 291-302.

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