

THE NGF IS WIDER THAN THE NEURON

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INTRODUCTION

On 15-19 May 2000 was held in Modena, Italy, The 7th International Conference on NGF and Related Molecules. The NGF2002 Conference emphasized the increasing significance of neurotrophins and related molecules in a variety of neuronal and nonneuronal functions and disorders. Luigi Aloe from Rome and Laura Calzà from Bologna, functioning as Chairman and Vice Chairman, did a superb job of organizing the Conference. More than 200 participants were "housing in enriched environment" in the Castle of the Doge's Palace (for lecture sessions) and in Caffè Concerto at the beautiful Piazza Grande Modena, for poster session. The meeting began with the talk of the Nobel Laureate Rita Levi-Montalcini (see manuscript "NGF and the neuroscience chess board" in this issue).

The Conference highlighted different aspects of our current understanding of neurotrophin-receptor signal transduction pathways (P.A. Barker, Montreal; M. Bothwell *et al.*, Seattle; M. Chao *et al.*, New York; M. Fainzilber *et al.*, Rehovot, Stockholm, Edinburg; E.M. Johnson Jr *et al.*, St Louis; D. Kaplan and F. Miller, Montreal; B.B. Rudkin *et al.*, Lyon, San Francisco; L.F. Reichardt, San Francisco; B.D. Carter *et al.*, Nashville, Yokohama; J.X. Comella *et al.*, Spain; J.J. Gentry *et al.*, Nashville; H. Heerssen *et al.*, Boston; R. Heumann *et al.*, Leipzig; S. Suzuki *et al.*, Osaka; L. Minichiello *et al.*, Heidelberg, Tubingen, Hamburg, Berlin, Monterotondo, Nebraska, Cleveland; W.J. Friedman *et al.*, New York, Rehovot), including the signaling endosome hypothesis (W.C. Mobley *et al.*, Stanford; A. Kruttgen *et al.*, Bern, Stanford; F. Bronfman *et al.*, Rehovot; C. Zurzolo *et al.*, Napoli). Emerging findings on the synaptotrophic potential of NGF and related neurotrophins (I. Black *et al.*, New Jersey; B. Lu, Bethesda; T. Tsumoto, Osaka; M. Kojima *et al.*, Osaka), neurotrophin involvement in neuronal stem cell biology (J. Angelastro *et al.*, New York, Gainesville; L. Calzà *et al.*, Bologna, Modena; P. Triaca *et al.*, Rome; M. Doring *et al.*, Philadelphia, for VEGF; J.A. Kessler *et al.*, Chicago, Bronx, for BMP-4; A. Chalazonitis *et al.*, Chicago, Bronx, for BMP-2,-4), biological activity of the NGF precursor proNGF (M. Fahnstock *et al.*, Hamilton; B. Hempstead, New York; S.O. Yoon *et al.*, Columbus, New York), and nociception- and antinociception-associated activity of NGF and/or BDNF (T. Lundberg, Stockholm; S.B. McMahon, London; A. Merighi *et al.*, Torino, Padova) were also presented and discussed. Receptor signaling by members of the GDNF family was also highlighted (C.F. Ibanez, Stockholm; M. Lindahl *et al.*, Helsinki, New York; A. Popsueva *et al.*, Helsinki; P. Runeberg-Roos *et al.*, Helsinki; B.A. Tsui-Pierchala *et al.*, St Louis; J. Milbrandt, St Louis).

NONNEURONAL NGF

During some 25 years after the discovery of NGF there have been few reasons given to indicate that NGF acts on nonneuronal cells. Thus, it was remarkable to discover that treatment of rats with NGF caused a significant increase in the number of mast cells in various tissues. This seminal finding, published by Luigi Aloe and Rita Levi-Montalcini in *Brain Research* 1977; 133: 358-366, has triggered the study on nonneuronal activities of NGF, particularly, NGF-based neuroimmune communication. Such immunotrophic actions of NGF, also other neurotrophic factors subsequently discovered, opened a novel avenue in the study of neurobiology, namely, the basic and clinical neuroimmunology. Thus we witness an exciting time in the field of integrative physiology. Accordingly, several presentations at the Modena NGF2002 Conference dealt with the involvement of various neurotrophins in the control of different nonneuronal processes, such as immune, inflammatory and allergic reactions (L. Bracci-Laudiero *et al.*, Rome; P. Lazarovici *et al.*, Jerusalem; F. Levi-Schaffer *et al.*, Jerusalem, Rome; N. Frossard, Illkirch; S.P. Raychaudhuri and S.K. Raychaudhuri, Pal Alto; Celestino *et al.*, Rome; H. Renz, Marburg;), angiogenesis (P. Madeddu *et al.*, Osilo, Rome; P. Turrini *et al.*, Rome; A. Chiaretti *et al.*, Rome), tissue repair/wound healing (H. Matsuda, Tokyo; L. Aloe and A. Lambiase, Rome; P. Rama *et al.*, Rome, Milan; A. Micera *et al.*, Jerusalem, Rome), and even hair growth (R. Paus, Hamburg; M. Grim *et al.*, Milwaukee, Prague). These findings showed that neurotrophins play important roles in the pathobiology of a surprising variety of seemingly unrelated nonneurological diseases, including bronchial asthma, rheumatoid arthritis, atherosclerosis, metabolic syndrome, congenital cardiac malformation, breast cancer, crush syndrome, Behçet's disease, hair growth disorders, and cutaneous and corneal ulcers.

Also presented at Modena NGF2002 were important new findings on the involvement of NGF and related molecules in neurological diseases, including Huntington's disease (J. Alberch *et al.*, Barcelona), the multiple sclerosis-like model of experimental allergic encephalomyelitis (C. Genain, San Francisco; B. Oderfeld-Nowak *et al.*, Warsaw, Rome; L. Calzà *et al.*, Bologna, Modena; H. Wekerle, Berlin), peripheral neuropathies (P. Anand and D.V. Sinicropi, London, San Francisco), inherited retinopathy (T. Amendola and L. Aloe, Rome), neuroblastoma (A. Nakagawara, Chiba), brain tumors (A. Antonelli *et al.*, Rome), epilepsy (S. Lähteinen *et al.*, Kuopio; Y. Larmet *et al.*, Strasbourg; E. Tongiorgi *et al.*, Trieste, Ferrara), Alzheimer's disease (G. Della Valle *et al.*, Bologna, Verona; J.B. Tuttle *et al.*, Charlottesville; J. Diamond *et al.*, Hamilton, Montreal), Parkinson's disease (J.B. Tuttle *et al.*, Charlottesville; J.W. Commissiong *et al.*, Toronto, for mesencephalic astrocyte-derived neurotrophic factor), spinal cord injury (L. Olson, Stockholm; J. Verhaagen, Amsterdam; J.C. Boyd *et al.*, Kingston, Saskatoon; S.O. Yoon *et al.*, Columbus, New York), traumatic brain injury (Chiaretti *et al.*, Rome), and even motion sickness syndrome (D. Santucci *et al.*, Rome), also psychiatric disorders (M. Fiore and J. Korf, Rome, Groningen), including depression (F. Angelucci and A.A. Mathe, Stockholm, Rome; E. Castrén *et al.*, Kuopio).

THERAPEUTIC NGF

Other important findings emerged at the Modena NGF2002 Conference were that the administration, to patients or experimental animals with at least certain of these diseases, of NGF or NGF/Trk A and/or NGF/p75 antagonists, are likely to exert important therapeutic benefits. For example, Dr P. Anand from London presented a talk entitled "how can we make them work?", which described ongoing clinical trials using rhNGF, rhBDNF, and rhNT-3 in diabetic neuropathy and gastrointestinal dysmotility, also CNS neurodegenerative disease (C. Genain, San Francisco, for rhNGF in experimental allergic encephalomyelitis). And, Dr Karen Philpott et al from GlaxoSmithKline in Harlow, UK focused on the search for small molecules as drugs targeting modulation of neurotrophic factor receptor signaling in neurodegenerative disease. Additionally, Luigi Aloe's group from Rome presented important findings on the beneficial effects of topically applied NGF in human cutaneous and corneal ulcers, as well as on the beneficial effect of NGF treatment in peripheral ischemic vasculopathy (apparently due to its angiogenic activity). An additional sub-theme of the Conference was that the neurotrophins could act to upregulate some hidden actions of drugs that are already in wide clinical use. For example, R. Bernardini *et al.* (Catania, Jerusalem) demonstrated that the antiestrogen drug tamoxifen inhibited NGF-induced cell proliferation in human breast cancer cell line; F. Angelucci and A.A. Mathe (Stockholm, Rome) and E. Castrén *et al.* (Kuopio) presented data suggesting that neurotrophins may be involved in the therapeutic potential of antidepressant drugs; and L. Giardino *et al.* (Bologna, Milan, Rome, Modena) implicated increased expression of NGF and BDNF in the neuroprotective effect of nicergoline (sermion). It is worth reminding here that aspirin kept hidden its antiplatelet therapeutic action until the discovery of prostanoids; likewise, pentoxifylline (trental) revealed its anti-TNF- α anti-inflammatory potential due to the advancement in cytokine research. Then why not look for some "old" drugs to disclose their neurotrophic factor-mediated therapeutic potential?

In effect, the Conference raised many intriguing leads about how novel, neurotrophin-targeted therapies could develop in the near future. In a similar vein, several talks from groups as widespread as B. Oderfeld-Nowak *et al.* from Warsaw and Rome, P. Lazarovici *et al.* from Jerusalem, Rehovot, and Bazel, and H. Wekerle from Berlin suggested that the secretion of neurotrophins by T-cells invading the CNS (which has been dubbed "neuroprotective autoimmunity") may have potential therapeutic implications for neuroimmune diseases such as multiple sclerosis. These new findings, as well as a lot of other valuable data presented at the Conference that we unfortunately do not have space here to discuss, left the Conference's participants with the general idea that the actions of neurotrophins are complex and diverse, and that they need to design many new studies to determine how these agents can, under different conditions, both promote and suppress various processes mediated by autoimmunity, inflammation, and allergy. Overall, this cultivated much a new thinking about the therapeutic potentials of various neurotrophic factors.

CONCLUSION

All the events included in the program of NGF2002 were shared by the constant presence of Professor Rita Levi-Montalcini, herself. As often occurs, the framework of an initial conception of the physiological significance of newly discovered molecule extends in the light of emerging findings. Clearly, NGF is one of the most exciting examples of this intellectual growth process. Conceived originally as no more than a growth and survival factor for certain neuronal cells, within the last 50 years, Levi-Montalcini's students and disciples dispersed all over the world have been passing the torch of NGF research from generation to generation.

The NGF2002 conference demonstrated highly graphically how NGF and its relatives, in addition to their neurotrophic activities, also exert important and often critical immunotrophic, epitheliotrophic, and inflammation-, allergy- and tissue repair-associated activities. Paraphrasing Emily Dickinson's poem *The brain is wider than the sky*, when Rita Levi-Montalcini discovered NGF more than 50 years ago, could she possibly have imagined that *the NGF is wider than the neuron*? Indeed, it is extremely rare one scientist to so much valuably contribute to the development of a research field, as she has been doing! Doubtlessly, many new findings on NGF will emerge in the next two years, and will further enrich Rita Levi-Montalcini's Saga of the NGF.