Biomedical Reviews 2002; 13: 67-69.

ISSN 1310-392X

MEETING REVIEW

NGF2002: MORE POWERFUL THAN NGF1951

In 1951, Rita Levi-Montalcini discovered nerve growth-stimulating factor, later named nerve growth factor (NGF), which today is recognized as the paradigm of a whole family of neurotrophic proteins, the neurotrophins. Half a century later, on 15-19 May, 2002, in Modena, Italy, The 7th International Conference on NGF and Related Molecules celebrated this *tour de force* of NGF's discovery, by presenting the state-of-the-art in neurotrophic factor research, including 60 lectures and 75 posters from world experts in neurotrophobiology, including, most notably, Rita Levi-Montalcini herself from Italy, as well as E. Shooter, M. Chao, L. Green, E. Johnson Jr, L. Parada, B. Hempstead, L. Reichardt and W. Mobley from the USA, D. Kaplan and J. Bienenstosk from Canada, H. Thoenen, R. Paus and K. Unsicker from Germany, L. Olson, T. Lundeberg and C. Ibanez from Sweden, H. Matsuda and A. Nakagawara from Japan, M. Fainzilber and P. Lazarovici from Israel, S. Lahteinen from Finland, and R. Rush from Australia.

Since the first meeting held in 1986 in Monterey, USA, Members of the International Scientific Committee, E. Shooter and R. Bradshaw from USA and R. Rush from Australia, succeeded admirably in promoting this biannual meetings, which encourages and facilitates the free and sometimes provocative expression and exchange of ideas. The Modena 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 Calza from Bologna, functioning as Chairman and Vice Chairman, did a superb job of organizing the Conference. More than 200 participants were "housed in enriched environment" in the Castle of the Doge's Palace that certainly resulted in an increase in the brain levels of NGF, BDNF and NT-3 (Mohammed, Huddinge). Further, participants' feeding behavior was provoked by the delicious local cuisine, including parmigiano cheese and red wine, that, *via* the gastric hormone cholecystokinin-8 (Tirassa *et al*, Rome, Stockholm; Bucinskaite *et al*, Stockholm, Rome, Ohtawara) and certain probiotics (Bienenstock and Ma, Hamilton), also might have contributed to the elevated amount of brain and gastrointestinal NGF, respectively. The only gripe among some participants was that they seemed to take too seriously the recent findings of their colleagues Iannitelli *et al* (Rome), concerning NGF's ultradian cycle in humans. This work, showing that NGF plasma levels are highest in the morning, apparently stimulated the organizers to schedule conference sessions to begin at 8AM, a brutally early hour, considering the many liquid evenings spent in Modena. Note that these may induce motion sickness syndrome due to rotation, hypergravity-like reactions leading to significantly increased expression of NGF in hypothalamus, hippocampus, olfactory bulbs and in both frontal and parietal cortex (Santucci *et al*, Rome).

The Modena NGF2002 meeting began with the talk of the Nobel Laureate Rita Levi-Montalcini on "NGF and the neuroscience chess board". After reviewing the major NGF findings, she hypothesized that the role of NGF may be likened to that of the "pawn" on the real chess board. She suggested that: "In the neuroscience chess board the genes involved in functions which were considered in the past of second order such as that of the "pawns" of the real chess board, program the release of chemical substances, which intervene in the complicated nervous and non-nervous functions of all vertebrates, from the lowest to the highest phylogenetic level. One of these substances is the NGF."

The Conference highlighted different aspects of our current understanding of neurotrophin-receptor signal transduction pathways (Barker, Montreal; Bothwell *et al*, Seattle; Chao *et al*, New York; Fainzilber *et al*, Rehovot, Stockholm, Edinburg; Johnson Jr *et al*, St Louis; Kaplan and Miller, Montreal; Rudkin *et al*, Lyon, San Francisco; Carter *et al*, Nashville, Yokohama; Comella *et al*, Spain; Gentry *et al*, Nashville; Heerssen *et al*, Boston; Heumann *et al*, Leipzig; Suzuki *et al*, Osaka; Kruttgen *et al*, Bern, Stanford; Minichiello *et al*, Heidelberg, Tubingen, Hamburg, Berlin, Monterotondo, Nebraska, Cleveland; Friedman *et al*, New York, Rehovot), including the signaling endosome hypothesis (Mobley *et al*, Stanford; Kruttgen *et al*, Bern, Stanford; Bronfman *et al*, Rehovot, Göettingen; Zurzolo *et al*, Napoli). Also presented were the synaptotrophic potential of NGF and related neurotrophins (Black *et al*, New Jersey; Lu, Bethesda; Tsumoto, Osaka; Kojima *et al*, Osaka), neurotrophin involvement in neuronal stem cell biology (Angelastro *et al*, New York, Gainesville; Calza *et al*, Bologna; Triaca *et al*, Rome; During *et al*, Philadelphia, for VEGF; Kessler *et al*, Chicago, Bronx, for BMP-4; Chalazonitis *et al*, Chicago, Bronx, for BMP-2,-4), biological activity of the NGF precursor proNGF (Fahnestock *et al*, Hamilton; Hempstead, New York; Yoon *et al*, Columbus), and nociception- and antinociception-associated activity of NGF and/or BDNF (Lundeberg, Stockholm; McMahon, London; Merighi *et al*,

Torino, Padova). Receptor signaling by members of the GDNF family was also highlighted (Ibanez, Stockholm; Lindahl *et al*, Helsinki, New York; Popsueva *et al*, Helsinki; Runeberg-Roos *et al*, Helsinki; Tsui-Pierchala *et al*, 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 (Bracci-Lauiero *et al*, Rome; Lazarovici *et al*, Jerusalem; Levi-Schaffer *et al*, Jerusalem, Rome; Frossard, Illkirch; Raychaudhuri and Raychaudhuri, Palo Alto; Celestino *et al*, Rome; Renz, Marburg; Pignatti *et al*, Modena), angiogenesis (Madeddu *et al*, Osilo, Rome; Turrini *et al*, Rome), tissue repair/wound healing (Matsuda, Tokyo; Aloe and Lambiase, Rome; Rama *et al*, Rome, Milan; Micera *et al*, Jerusalem, Rome), and even hair growth (Paus, Hamburg; Grim *et al*, Milwaukee, Prague). These findings showed that neurotrophins play important roles in the pathobiology of a wide range of seemingly unrelated diseases (Table).

Also presented at Modena NGF2002 were important new findings on the involvement of NGF and related molecules in neurological diseases, including Huntington's disease (Alberch *et al*, Barcelona), multiple sclerosis (Althaus, Göttingen), including its models, experimental allergic encephalomyelitis

Table. *NGF and other neurotrophins in nonneurological diseases*

Diseases	Authors
Bronchial asthma	Frossard, Illkirch Renz, Marburg Braun *et al*, Hannover, Marburg
Cutaneous ulcers	Aloe and Lambiase, Rome Matsuda, Tokyo Manni *et al*, Florence, Rome, Oristano Anand and Sinicropi, London, San Francisco
Allergic and ulcerative eye disorders	Levi-Schaffer *et al*, Jerusalem, Rome Rama *et al*, Rome, Milan Coassin *et al*, Rome, Milan
Behcet's disease	Bruscolini *et al*, Rome
Colitis	Bienenstock and Ma, Hamilton
Hair growth disorders	Paus, Hamburg
Psoriasis	Raychaudhuri and Raychaudhuri, Palo Alto
Breast cancer	Bernardini *et al*, Catania, Jerusalem
Crush syndrome	Chiaretti *et al*, Rome
Atherosclerosis	Hempstead, New York Chaldakov *et al*, Varna, Rome
Peripheral ischemic vascular disease	Madeddu *et al*, Osilo, Rome Turrini *et al*, Rome
Persistent truncus arteriosus	Sieber-Blum *et al*, Milwaukee, Frederick, Osaka

(Genain, San Francisco; Oderfeld-Nowak *et al*, Warsaw, Rome; Zaremba *et al*, Warsaw, Rome), peripheral neuropathies (Anand and Sinicropi, London, San Francisco), inherited retinopathy (Amendola and Aloe, Rome), neuroblastoma (Nakagawara, Chiba), brain tumors (Antonelli *et al*, Rome), epilepsy (Lahteinen *et al*, Kuopio; Larmet *et al*, Strasbourg; Tongiorgi *et al*, Trieste, Ferrara), Alzheimer's disease (Della Valle *et al*, Bologna, Verona; Tuttle *et al*, Charlottesville; Diamond *et al*, Hamilton, Montreal), Parkinson's disease (Tuttle *et al*, Charlottesville; Commissiong *et al*, Toronto, for mesencephalic astrocyte-dervied neurotrophic factor), spinal cord injury (Olson, Stockholm; Verhaagen, Amsterdam; Boyd *et al*, Kingston, Saskatoon), traumatic brain injury (Chiaretti *et al*, Rome), and even motion sickness syndrome (Santucci *et al*, Rome), also psychiatric disorders (Fiore and Korf, Rome, Groningen), including depression (Angelucci and Mathe, Stockholm, Rome; Castren *et al*, Kuopio).

THERAPEUTIC NGF

Another viewpoint that clearly emerged at the Modena NGF2002 Conference was that the administration NGF and/or NGF/Trk A or NGF/p75 antagonists to patients or experimental animals with at least certain of the above-mentioned diseases, are likely to exert important therapeutic benefits. For example, 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. And, Karen Philpott *et al* from GlaxoSmithKline in Harlow 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 (effects that are apparently due to NGF's anti-inflammatory and tissue-repairing activities), as well as presenting findings on the beneficial effects of topically applied NGF in peripheral ischemic vasculopathies (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, Bernardini *et al* (Catania, Jerusalem) demonstrated that the antiestrogen drug tamoxifen inhibited NGF-induced cell proliferation in human breast cancer cell line; Angelucci and Mathe (Stockholm, Rome) and Castren *et al* (Kuopio) presented data suggesting that neurotrophins may be involved in the therapeutic potential of antidepressant drugs; and Giardino *et al* (Bologna, Milan, Rome, Modena) implicated increased expression of NGF and BDNF in the neuroprotecive effect of nicergoline (sermion). It is worth reminding here that aspirin kept hidden its anti-platelet therapeutic action until the discovery of prostanoids; likewise, pentoxifylline revealed its anti-TNF/anti-inflammatory potential due to the advancement in cytokine research. Then why not look for other "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, talks from Oderfeld-Nowak *et al* from Warsaw and Rome, Lazarovici *et al* from Jerusalem, Rehovot and Bazel, and 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 to discuss here, 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 vital 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.

In conclusion, NGF2002 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 for one scientist to contribute so much to the development of a research field, as she has done!

Arrivederci, the Modena NGF2002 Conference! 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*.

ACKNOWLEDGMENTS

Creative reading of the manuscript by Dr John Heuser is highly appreciated.

George N. Chaldakov
Invited Observer at the 7th International NGF
and Related Molecules Conference
Medical University
Varna, Bulgaria