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Supplementary Information for

Fall of the Titans

The Demise of Basic Neuroscience Research

By Sergio Canavero* and Vincenzo Bonicalzi

Table S1. *Science* 1990.

No.	Date	Authors	Start page	Model	Disease/activity	Authors' conclusions
1	February 2	Sheardown et al.	571	Mice/ biochemistry	Neuroprotection	NBQX is a highly sensitive non-NMDA excitatory amino acid receptor antagonist that can act as neuroprotectant in global ischemia.
2		Lindvall et al.	574	Man (case report)	Parkinson's disease	Neural grafting can be developed with further work into an effective therapy in Parkinson's disease.
3	March 23	Maisonpierre et al.	1446	Biochemistry/ cell culture	Neuroprotection	Animal studies have suggested that NGF may be of value in the treatment of degenerative neurological conditions. The cloning of a new member of the NGF-BDNF family, and its potential interactions with the other members of the family, raise new considerations for use of these proteins in overcoming neuronal degeneration.
4		Wolff et al.	1465	Mouse/ biochemistry	Muscle diseases	If direct transfer of genes into human muscles in situ also occurs, it may have several potential clinical applications. The effects of genetic diseases of muscle might be ameliorated by expression of the normal gene within muscle cells. Muscle might also be a suitable tissue for the heterologous expression of a transgene that would modify disease states in which the muscle is not primarily involved…[and] prpvide alternative approaches to vaccine development…[and] a reversible type of gene transfer, administered much like conventional pharmaceutical treatments.
5		Weiss et al.	1474	Cell culture/ biochemistry	Neuroprotection	Our *in vitro* observations suggest that dihydropyridines (nifedipine, nimodipine) could have therapeutic value in disease states characterized by slow glutamate neurotoxicity. Our observations add support to the idea that some types of excitoxicity can be attenuated by pharmacological approaches directed at targets other than glutamate receptors.
6	April 13	Kaas et al.	229	Cats	Neuroplasticity	Adult plasticity (in the CNS) may be important…in our abilities to maintain, alter, and improve sensorimotor and perceptual skills.
7	May 25	Wucherpfennig et al.	1016	Biochemistry/ men	Multiple sclerosis	These data demonstrate shared T cell receptor Vβ gene usage in humans to an immunodominant region of the autoantigen MBP. This may help in the design of new specific therapeutic approaches for MS.
8	June 15	Rich and Hollowell	1419	Cell culture/ mice/ biochemistry	Neuroprotection	Our data indicate that neuronal death after neurotrophic deprivation can be prevented by flunarizine *in vivo* and *in vitro*… such pharmacological agents have promise in future clinical approaches.
9	September 21	Bergman et al.	1436	Monkeys	Parkinson's disease	Our results suggest a potential clinical application for surgical or pharmacological inactivation of the subthalamic nucleus as a treatment for Parkinson's disease. However, further studies in experimental animals are necessary to examine the long-term effects of STN lesions (!) and possible interactions with drug treatment.
10	October 12	Yankner et al.	279	Cell culture/ biochemistry	Alzheimer's disease	If amyloid β protein neurotoxicity proves to be relevant to the pathogenesis of Alzheimer's disease, the reversal of neurotoxicity by tachykinins could have clinical import.
11	December 7	Gerfen et al.	1429	Rats	Parkinson's disease	Intermittent injections of a dopamine 1 agonist appear necessary to produce regulation of striatonigral neurons, whereas continuous treatment with a D2 agonist appears necessary to regulate striatopallidal neurons in Parkinson's disease.

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Table S2. ***Science*** **2000.**

No.	Date	Authors	Start page	Model	Disease/activity	Authors' conclusions
1	February 25	During et al.	1453	Rats	Neuroprotection	A stroke PO vaccine against NMDAR1 may hold promise as a prophylactic measure to protect the brain. Moreover, the ability of systemic immunization to generate autoantibodies which alter the function of native brain proteins opens up a new avenue for modulating the nervous system and treating neurological and psychiatric disorders.
2		Priola et al.	1503	Hamsters, mice	Prion diseases (diabetes)	Optimization of tetrapyrrole structure for prophylactic or even therapeutic effectiveness among this class of anti-transmissible spongiform encephalopathies agents is especially promising. Cyclic tetrapyrroles may provide a basis for therapeutic approaches for Alzheimer disease or type 2 diabetes.
3	March 10	Kazemi-Esfarjani and Benzer	1837	*Drosophila*	Huntington's chorea	Discovery of suppressor genes of polyglutamine toxicity may lead to the discovery of other genes relevant to various polyglutamine disorders—e.g. Huntington's chorea—and their prophylactic or therapeutic treatment.
4	March 17	Castner et al.	2020	Monkeys	Schizophrenia	Schizophrenic patients now treated with dopamine D2 antagonist drugs may show substantial improvements in their cognitive abilities from a limited exposure to a D1 agonist (ABTh31).
5	April 14	Caterina et al.	306	Mice	Pain	Vanilloid (capsaicin) receptor VR1 represents a potential therapeutic target for treating specific conditions that arise with tissue damage.
6		Li et al.	335	Mice	ALS	Therapy directed at inhibiting caspase function should begin in the presynaptic stage of ALS.
7	April 21	Lowrey et al.	483	Hamster	Circadian rhythms	As such, casein kinase Iε (CKIε) makes an ideal target for pharmaceutical compounds influencing circadian rhythms, sleep and jet lag, as well as other processes under circadian regulation.
8	April 28	Brzustowicz et al.	678	Humans	Schizophrenia	It is hoped that a better understanding of the genetic factors involved in schizophrenia will lead to earlier and more effective interventions.
9	May 19	Montrasio et al.	1257	Mice	Prion diseases	Long-term treatment with lymphotoxin β receptor-Ig could retard progression of prion diseases.
10	July 14	López-Coviella et al.	313	Biochemistry	Neurodegenerative diseases	The action of BMP (bone morphogenetic protein)-9 as a cholinergic differentiation factor suggests its potential use in the treatment of diseases that affect cholinergic neurons.
11	July 28	Kaneko et al.	633	Biochemistry	Parkinson's disease	A persistent restraint in Ach actions impairs a modulatory effect of dopamine transmission in the basal ganglia circuit through a convergent Ach-DA interaction. Careful management of Ach antagonists is thus necessary for the treatment of Parkinson's disease.
12	September 8	Kondo and Raff	1754	Biochemistry, stem cells	Multiple sclerosis	The use of extracellular signal molecules to reprogram specified precursor cells in culture to become multipotential stem cells may prove useful for cell therapy of multiple sclerosis.
13	October 6	Boucher et al.	124	Rats	Pain (neuropathic)	The data provide a rational basis for, and demonstrate the efficacy of, GDNF in the treatment of neuropathic pain.
14		Löw et al.	131	Mice	Anxiety disorders	α2 GABA A receptors are highly specific targets for the development of future selective anxyolytic drugs.
15		Hong et al.	150	Biochemistry	Alzheimer's disease	The well-defined subsite structures spanning P4 to P2′ provide a template for rational design of drugs against memapsin 2. the unusual conformation of subsites P2′, P3′ and P4′ may facilitate the design of inhibitors selective for memapsin 2 (beta secretase).
16	October 27	Kordower et al.	767	Primates	Parkinson's disease	Lentiviral delivery of GDNF may provide potential clinical benefit for patients with Parkinson disease.
17	November 3	Giasson et al.	985	Biochemistry	Neurodegenerative diseases	Results suggest that impairment of cellular antioxidative mechanisms or overproduction of reactive species may be a primary event leading to the onset and progression of neurodegenerative synucleinopathies. Thus, elucidation of the role of oxidative and nitrative injury in mechanisms underlying these and other neurodegenerative disorders may lead to the identification of therapeutic targets to prevent or reverse these diseases.

Table S2 (*continued*)

No.	Date	Authors	Start page	Model	Disease/activity	Authors' conclusions
18	December 1	Hoek et al.	1768	Mice	Alzheimer's disease (hematology)	That these effects appear to be unrelated to T cell activation but rather the result of direct deregulation of effector pathways within the macrophage/myeloid lineage has important and broad implications for treatment of neurodegenerative diseases like Alzheimer's disease or for varied pathologies involving hyperactivation of the myeloid lineage.
19		Brazelton et al.	1775	Mice	Parkinson's disease, others	The generation of neuronal phenotypes in the adult brain 1 to 6 months after an adult bone marrow transplant demonstrates a remarkable plasticity of adult tissues with potential clinical applications. Thus, our findings are not only of fundamental interest but also, once more robust, could have application as a cell-mediated therapy. Not only could neurons be contributed to the adult brain, but, if genetically engineered, they could be a potentially useful tool for treating disorders characterized by defective neuronal function or a loss of neurons such as Parkinson's disease, lysosomal storage disorders, psychiatric disorders, trauma, and other types of CNS injury.
20		Mezey et al.	1779	Mice (transgenic)	Neurodegenerative diseases	These findings raise the possibility that bone marrow-derived cells may provide an alternative source of neurons in patients with neurodegenerative diseases or central nervous system injury. Bone marrow cells might be expanded *in vitro* and provide an unlimited source of cells for the treatment of CNS disease and injury.

Table S3. *Nature* 1990.

No.	Date	Authors	Start page	Model	Disease/activity	Authors' conclusions
1	January 11	England et al.	180	Biochemistry	Muscle diseases	These results are particularly significant in the context of gene therapy which, if it is ever envisaged, would be facilitated by the replacement of the very large dystrophin gene with a more manipulable mini-gene construct. …The "minigene" which functions so effectively in these patients should allow us to… assist in the development of ways to treat the disease (muscular dystrophy) in the future.
2	February 1	Caceres and Kosik	461	Biochemistry, cell culture	Alzheimer's disease	The inhibition induced by antisense oligonucleotides could serve as a basis for strategies to reduce the abundant tau-immunoreactive neuritis observed in Alzheimer's disease.
3	May 24	Oksenberg et al.	344	Biochemistry	Multiple sclerosis	Our results may prove to have therapeutic implications. ...Elucidation of [T cells antigen receptor] expression in the brain may help in the design of…treatment in MS patients.
4		Hughes and Blau	350	Rats	Muscle diseases	…injection of myoblasts into a few sites could constitute an efficient therapy for large regions of diseased muscle.
5	May 31	Sendtner et al.	440	Rats	Motor neuron disease	The observation that motor neurons' death can be prevented after lesion...could introduce novel therapeutic approaches to the treatment of motor neuron degeneration…it will be of interest to investigate whether CNTF also protects against toxic or genetic degenerative changes in motor neurons, and possibly also in those motor neuron disease of unknown aetiology.
6	August 16	Lüddens et al.	648	Biochemistry	Sundry	The correct recombinant re-creation of the new GABA-A receptor subtype may allow the development of new ligands for modulating channel activity at this neurophysiologically unique receptor subtype.
7	September 13	Sokoloff et al.	146	Biochemistry	Sundry	The molecular cloning of the D2 and D3 receptors should facilitate the design of more discriminant drugs…Such drugs may constitute safer and more effective therapeutic agents in psychiatry and neurology.
8	October 11	Wictorin et al.	556	Rats	Neuroregeneration	The extensive pathway-forming capacity of the slowly developing human neuroblast should provide new possibilities for the analysis of the cellular interactions underlying successful regeneration in the CNS.

Table S4. ***Nature*** **2000.**

No.	Date	Authors	Start page	Model	Disease/activity	Authors' conclusions
1	January 6	Nakagawa et al.	98	Mice	Alzheimer's disease	The human analogue of caspase-12 may be a potential therapeutic target for Alzheimer's disease.
2	January 20	Liu et al.	274	Cell culture	Sundry	Data indicate a potential therapeutic avenue of GABA A-Dopamine D5 mutually inhibitory modulation for psychomotor and neuropsychiatric disease states known to be defective in both GABAergic and dopaminergic tone.
3		Ramer et al.	312	Rats	Neuroregeneration	GDNF and other neurotrophic factors have vast therapeutic potential in the treatment of dorsal root lesions and of CNS damage in general.
4	January 27	Prinjha et al.	383	Cell culture	Neuroregeneration	The availability of active recombinant Nogo isoforms should help in the identification of their receptors. Such definition is critical for the development of pharmacologic treatments that will allow repair of lesions of the CNS.
5	March 2	Baker et al.	84	Mice	Multiple sclerosis (symptoms)	The data presented here provide evidence for the rational assessment of cannabinoid derivatives in the control of spasticity and tremor in multiple sclerosis, in placebo-controlled trials. The observation that CB1 appears to be the main therapeutic target suggests that it may be difficult to dissociate the full benefit from undesirable psychoactive elements using Δ9-THC or cannabis. The use of selective CB2 agonists may provide some symptomatic benefit without significant psychoactive effects. Furthermore, it may be possible to upregulate endogenous produced cannabinoids to mediate therapeutic benefit.
6	March 23	Feany and Bender	394	*Drosophila* (expression of normal and mutant forms of α-synuclein)	Parkinson's disease	Our *Drosophila* model…recapitulates the essential features of the human disorder, and makes possible a powerful genetic approach to Parkinson's disease.
7	April 13	Van Dellen et al.	721	Mice (transgenic)	Huntington's chorea	Our findings suggest that occupational therapy based on the principles of environmental enrichment might delay the onset of Huntington's disease in humans as well.
8	May 11	Murtra et al.	180	Mice (NK1−/−)	Drug abuse	We conclude that substance has an important and specific role in mediating the motivational aspects of opiates and may represent a new pharmacological route for the control of drug abuse. Drugs that antagonize the actions of substance may be powerful new tools in both the treatment of opiate drug addiction and the prevention of relapse into drug taking.
9		Davis et al.	183	Cell culture, mice, (transegenic)	Pain	Pharmacological experiments using the VR1 antagonist capsazepine have also demonstrated an antihyperalgesic effect. Selective VR1 antagonists may therefore prove effective for the treatment of thermal hyperalgesia.
10	May 18	Lee et al.	360	Biochemistry, cells cultures (mice)	Alzheimer's disease	Given the potentially deleterious role of cdk5 in Alzheimer's disease, the calpain-mediated p35 cleavage pathway may serve as a target for pharmacological intervention.
11	June 22	Magavi et al.	951	Mice	Neuroregeneration	Our results indicate that neuronal replacement therapies for neurodegenerative disease and CNS injury may be possible through manipulation of endogenous neural precursors in situ. Our results indicate that it may be possible to manipulate endogenous neural precursors in situ to undergo neurogenesis in the adult brain. Elucidation of the relevant molecular controls may allow the development of neuronal replacement therapies for neurodegenerative disease and other CNS injury that do not require transplantation of exogenous cells.
12	July 13	Clarke et al.	195	Cells (mice, cultured, rat, cat, humans)	Neurodegenerative diseases	Our findings are most simply accommodated by a "one hit" biochemical model in which mutation imposes a mutant steady state on the neuron and a single event randomly initiates cell death. This model appears to be common to many forms of neurodegeneration and has implications for therapeutic strategies. The absence of cumulative damage means that the likelihood that a mutant neuron can be rescued by treatment is not diminished by age, although fewer cells will be available to rescue. Therefore, treatment at any stage of the illness is likely to confer benefit.
13	November 2	Fernandez-Funez et al.	101	*Drosophila* (human SCA1 gene)	Alzheimer's disease, Parkinson's disease	These findings may be relevant to the treatment of polyglutamine diseases and, perhaps, to other neurodegenerative diseases (caused by proteins), such as Alzheimer's and Parkinson's disease.

Table S4 (*continued*)

No.	Date	Authors	Start page	Model	Disease/activity	Authors' conclusions
14	November 9	Usiello et al.	199	Mice	Neuropathologies	D2L−/− mice could be used to develop drugs that can discriminate between D2S and D2L *in vivo*, leading to novel pharmacological strategies for the treatment of neuropathologies.
15	November 23	Fischer et al.	479	Biochemistry	Prion diseases	Lasminogen represents the first endogenous factor discriminating between normal and pathological prion protein. This unexpected property may be exploited for diagnostic purposes. If plasminogen depletion reduces the infectious load of prion-spiked plasma, it might be useful for improving prion removal from blood-derived biological products.
16	December 14	Morisset et al.	860	Cell culture, Mice	AD-HD, Alzheimer's disease	Activation of histaminergic neurons…has been proposed as a symptomatic therapeutic approach in human attentional and ageing disorders, such as attention-deficit hyperactivity disorders and Alzheimer's disease. Our observations indicate that such an effect is more likely to be obtained with H3-receptor inverse agonists rather than with neutral antagonists, as has been assumed so far.
17	December 21–28	Janus et al.	979	Mice	Alzheimer's disease	Our data support the hypotheses that Aβ plays a central role in Alzheimer's disease and that procedures (vaccination) that modulate its production, assembly and/or removal might be used as treatments.