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Review

Trackins (Trk-Targeting Drugs): A Novel Therapy for Different Diseases

George N. Chaldakov [1,*], Luigi Aloe [2], Stanislav G. Yanev [3], Marco Fiore [4,*], Anton B. Tonchev [1], Manlio Vinciguerra [5], Nikolai T. Evtimov [6], Peter Ghenev [7] and Krikor Dikranian [8]

1 Departments of Anatomy and Cell Biology and Translational Stem Cell Biology, Research Institute, Medical University, 9002 Varna, Bulgaria
2 Fondazione Iret, Tecnopolo R. Levi-Montalcini, Ozzano dell'Emilia, 40064 Bologna, Italy
3 Institute of Neurobiology, Bulgarian Academy of Sciences, 1113 Sofia, Bulgaria
4 Institute of Biochemistry and Cell Biology, National Research Council, IBBC-CNR, 00185 Rome, Italy
5 Department of Translational Stem Cell Biology, Research Institute, Medical University, 9002 Varna, Bulgaria
6 Department of Urology, University St Anna Hospital, 9002 Varna, Bulgaria
7 Department of General and Clinical Pathology, Medical University, 9002 Varna, Bulgaria
8 Department of Neuroscience, Medical School, Washington University, St. Louis, MO 63110, USA
* Correspondence: chaldakov@yahoo.com (G.N.C.); marco.fiore@cnr.it (M.F.)

Abstract: Many routes may lead to the transition from a healthy to a diseased phenotype. However, there are not so many routes to travel in the opposite direction; that is, therapy for different diseases. The following pressing question thus remains: what are the pathogenic routes and how can be they counteracted for therapeutic purposes? Human cells contain >500 protein kinases and nearly 200 protein phosphatases, acting on thousands of proteins, including cell growth factors. We herein discuss neurotrophins with pathogenic or metabotrophic abilities, particularly brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), pro-NGF, neurotrophin-3 (NT-3), and their receptor Trk (tyrosine receptor kinase; pronounced "track"). Indeed, we introduced the word *trackins*, standing for Trk-targeting drugs, that play an agonistic or antagonistic role in the function of $TrkB^{BDNF}$, $TrkC^{NT-3}$, $TrkA^{NGF}$, and $TrkA^{pro\text{-}NGF}$ receptors. Based on our own published results, supported by those of other authors, we aim to update and enlarge our *trackins concept*, focusing on (1) agonistic trackins as possible drugs for (1a) neurotrophin-deficiency cardiometabolic disorders (hypertension, atherosclerosis, type 2 diabetes mellitus, metabolic syndrome, obesity, diabetic erectile dysfunction and atrial fibrillation) and (1b) neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, and multiple sclerosis), and (2) antagonistic trackins, particularly $TrkA^{NGF}$ inhibitors for prostate and breast cancer, pain, and arrhythmogenic right-ventricular dysplasia. Altogether, the druggability of $TrkA^{NGF}$, $TrkA^{pro\text{-}NGF}$, $TrkB^{BDNF}$, and $TrkC^{NT-3}$ receptors via trackins requires a further translational pursuit. This could provide rewards for our patients.

Keywords: Trk-targeting drugs (trackins); Trk receptors; NGF; proNGF; BDNF; NT-3; cardiometabolic diseases; Alzheimer's disease; cancer; pain

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1. Introduction

Thus, the task is not so much to see what no one has yet seen but to think what nobody has yet thought about that which everybody sees.

Arthur Schopenhauer

The discovery of nerve growth factor (NGF) in 1951 by Rita Levi-Montalcini was the Rosetta stone in understanding neural differentiation, survival, and functions [1,2]. Life, at both the local and systemic levels, requires nutritional, immune, neurotrophic, and metabotrophic support. Many routes may lead to the transition from a healthy to a diseased phenotype. However, there are not so many routes to travel in the opposite direction; that is, therapies for cardiometabolic diseases (CMD), neurodegenerative diseases, and cancers,

thus extending human life expectancy and Quality of Life (QoL) [3–6]. The following pressing question thus remains: what are the pathogenic routes and how can they be counteracted for therapeutic purposes?

2. Neurotrophins and Their Receptors

At present, the neurotrophin family of proteins consists of NGF, pro-NGF, brain-derived neurotrophic factor (BDNF), pro-BDNF, neurotrophin-3 (NT-3), NT-4/5, and NT-6 [5,6]. Of these, NGF, pro-NGF, BDNF, and NT-3 are multifunctional proteins, which, in addition to their neurotrophic action, exert various extraneuronal effects directed to immune, endothelial, beta-pancreatic, muscle, epithelial, and other nonneuronal cells [3–10]. As well as the metabolism of lipids and carbohydrates, we named metabotrophic effects and metabotrophic factors (MTF) [5,6].

Neurotrophins elicit their outcomes via ligation to $p75^{NTR}$), the pan-neurotrophin receptor, and Trk receptors, namely, $TrkA^{NGF}$, $TrkA^{pro\text{-}NGF}$, $TrkB^{BDNF}$, $TrkB^{NT-4/5}$, and $TrkC^{NT-3}$. The acronym Trk intends for tyrosine receptor kinases vs. non-receptor tyrosine kinases, which have no transmembrane domain (Figure 1, Tables 1–3).

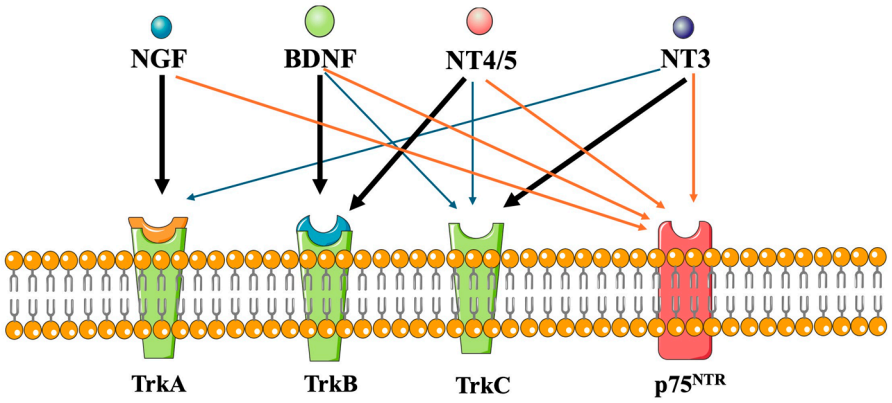

Figure 1. Neurotrophins and their Trk receptors. Redrawn from [11].

Table 1. Neurotrophin receptors and ligands. * Notably, the Trk receptor's transactivation through the G protein-coupled receptor has lately arisen as an original perspective on neurotrophin functions [12].

Receptors *	Neurotrophins
$p75^{NTR}$	NGF, BDNF, NT-3. NT-4/5
TrkA	NGF, pro-NGF
TrkB	BDNF, pro-BDNF, NT-4/5
TrkC	NT-3

Table 2. Multiple effects of NGF and BDNF. * Arrhythmogenic right-ventricular dysplasia (ARVD) is characterized by the accumulation and dysfunction of adipose tissue in the right ventricle of the heart, leading to ventricular arrhythmias and progressive right-ventricular failure, and often sudden cardiac death.

Physiotherapeutic	Pathogenic
Neurotrophic [13–16]	Oncotrophic (cancerogenic) [17–20]
Immunotrophic [21,22]	Nociceptogenic [23]
Metabotrophic [5,6,22]	Arrhythmogenic [24] *
Psychotrophic [20,25–30]	Pruritus [31,32]
Cognitogenic [33–42]	Dry-eye disease [43]
Angiogenic [44–53]	
Sperm vitality, mobility, fertility [54]	
Skin, cornea, axon and bone wound/fracture healing [31,32,43,55–70]	

Table 3. Metabotrophic effects of NGF and BDNF [5,6,22,54].

NGF and BDNF are released by pancreatic beta cells and have an insulinotropic effect
NGF has homology with proinsulin
BDNF-deficient mice may develop metabolic syndrome-like abnormalities
NGF up-regulates the expression of PPAR-gamma
NGF and BDNF are trophic factors for pancreatic beta cells
BDNF improves cognition
NGF up-regulates the expression of LDL receptor-related proteins
NGF increases skin and corneal wound healing
NGF inhibits glucose-induced down-regulation of caveolin-1
NGF increases diabetic erectile dysfunction
NGF may rescue silent myocardial ischemia in diabetes mellitus
A healthy lifestyle potentiates brain and/or circulating BDNF and NGF
An atherogenic diet reduces brain BDNF
BDNF potentiates cognitive processes
BDNF-deficient mice may develop abnormalities similar to the metabolic syndrome

In this connection, Figure 2 illustrates our own results of the potential significance of reduced local and/or blood levels of NGF and BDNF, functioning as metabotrophic factors (MTF) for the pathobiology of obesity and its related cardiometabolic and neurodegenerative diseases, particularly Alzheimer's disease (AD), with the latter being considered a neurometabolic disease [3–6,8–10,18].

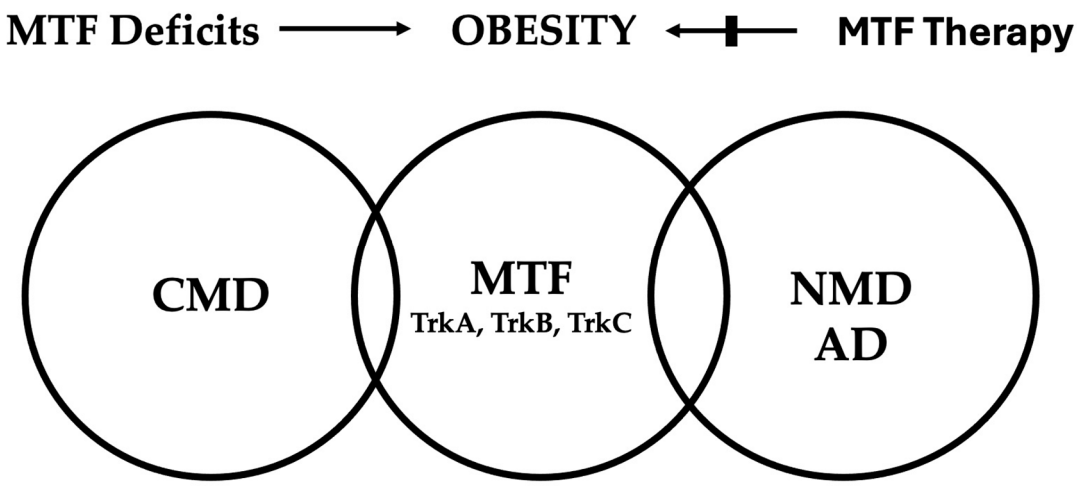

Figure 2. Metabotrophic factors (MTF) and their Trk receptors on the crossroads of the pathogenesis of and therapy for cardiometabolic diseases (CMD) and neurometabolic diseases (NMD), particularly Alzheimer's disease (AD). Credit Nikifor N. Chaldakov.

3. NGF, BDNF, and Their Trk Receptors: Druggable Targets for Disease Therapies

Druggability is a term used in drug discovery to describe biological targets [71,72]. In the context of the present article, these are the neurotrophins and their Trk receptors that are known or predicted to bind with high affinity to a drug [71,72]. Furthermore, by definition, the binding of the drug to a druggable target must alter the function of the target, with a therapeutic benefit to the patient [71,72]. The idea of druggability is most often constrained to low-molecular-weight chemicals (pharmaceuticals) but has also been revised

to include biologicals such as therapeutic monoclonal antibodies, and nutraceuticals such as polyphenols extracted from vegetables [73,74].

There are numerous pathways that can cause the transition from a healthy to a diseased phenotype. In contrast, the pathways to reverse this process, such as treating conditions like CMD and cancers to extend human life expectancy, are limited. The critical question is as follows: what are these pathogenic pathways, and how can they be effectively countered for therapeutic purposes?

Human cells contain >500 protein kinases and nearly 200 protein phosphatases acting on thousands of proteins including cell growth factors in health and disease; see [3,4]. At present, BDNF, NGF, and pro-NGF play a crucial role in the pathogenesis of a wide spectrum of neuronal and non-neuronal disorders, such as Alzheimer's and other neurodegenerative disorders, including obesity and related CMD [3,4,6]. The decreased presence of resident and/or blood circulating BDNF and NGF was described in metabolic syndrome, human coronary atherosclerosis, and acute coronary syndromes [3–7,9,10], suggestive of (i) a key function played by BDNF and NGF in the pathogenetic processes and (ii) a potential therapeutic action of $TrkB^{BDNF}$ and $TrkA^{NGF}$ receptor agonists in CMD. Indeed, it is well known that BDNF acts in the leptin-mediated anorexigenic circuit to regulate the adipose-brain regulation of food intake; see [5,6]. Mice heterozygous for BDNF-targeted disruption and mice with a reduced expression of the $TrkB^{BDNF}$ receptor show hyperphagia and obesity; see [4–6].

Notably, short-term myocardial ischemia produces a sympathetic cardiac innervation dysfunction associated with a rapid elevation in NGF release, while the NGF exogenous administration acts against such neuronal dysfunction, indicating that the endogenous production of NGF is inadequate for efficient neural protection [75]. Since reduced local and/or circulating levels of NGF and BDNF were found to be related to atherogenesis [3–10], the stimulation of $TkrA^{NGF}$ and $TrkB^{BDNF}$ receptors could create possible agonistic trackins with an anti-atherosclerotic effect.

Furthermore, recent studies show the therapeutic potential of NGF in the healing of corneal and cutaneous wounds [8,28,62,63,76,77], while $TrkA^{NGF}$ receptor antagonists have been studied for new drugs for prostate, breast, and other malignant tumors, as well as for pain [20,29,30,78]. Stromal cells of the prostate and adipose stromal cells secrete NGF, which, in a paracrine way, can stimulate the carcinogenic proliferation of prostatic epithelial cells [79]. In support of such data, chemical substances that inhibit $TrkA^{NGF}$ receptors are increasingly being investigated as potential anticancer drugs. For instance, $TrkA^{NGF}$ receptor expression is positively associated with the invasion and malignancy of cancer cells in the prostate, and its antagonist Lestaurtinib (codename CEP-701) was included in some clinical trials focusing on prostate cancer [80]. This drug is the chemical substance indolocarbazole that specifically inhibits the $TrkA^{NGF}$ receptor [19,80]. It should be noted that natural antibodies against NGF are also present in intravenous gammaglobulin (IVIg), which may inhibit the in vitro migration of prostate cancer cells; see [81]. Intriguingly, it was reported that tamoxifen, prescribed to breast cancer patients, may inhibit $TrkA^{NGF}$ phosphorylation and, respectively, the NGF-elicited proliferation of epithelial cells from breast cancer [82]. Reflecting on the phenomenon of repurposed drugs (such as aspirin and colchicine), the findings about tamoxifen align with numerous other instances where an old drug has been found to have a new use.

Another "danger" arises from data showing that NGF-induced increases in the sympathetic innervation of the myocardium are implicated in the pathobiology of sudden cardiac death [83]. We consider these latter results as suggestive of a probable participation of NGF and its TrkA receptor in the pathogenetic mechanisms of arrhythmogenic right-ventricular dysplasia [24]. This is a genetic type of cardiomyopathy, characterized histologically by the substitution of deteriorated cardiomyocytes with NGF/BDNF-produced adipocytes documented in our immunohistochemical study [24]. Despite this, the possibility of $TrkA^{NGF}$ and $TrkC^{NT-3}$ receptor antagonists possessing an anti-arrhythmogenic action remains to further be investigated.

Intriguingly, high-pressure treatment with sterile physiological saline isotonic solution into the nasal cavity of individuals with sensorineural hearing loss and tinnitus potentiates NGF levels (in the nasal fluid), leading to improved hearing [84]. "Paradoxically", recent experimental results obtained with a $TrkA^{NGF}$ receptor inhibitor, GW441756, suggest that one component of an optimal therapy for Alzheimer's disease may be a $TrkA^{NGF}$ antagonist [20].

4. Conclusions and Perspectives

> In science, the Apollonian tends to develop established lines to perfection, while the Dionysian rather relies on intuition and is more likely to open new, unexpected alleys for research. The future of mankind depends on the progress of science, and the progress of science depends on the support it can find. Support mostly takes the form of grants, and the present methods of distributing grants unduly favor the Apollonian.
>
> Albert Szent-Gyorgyi (1972), Nobel Prize winner 1937 in Physiology or Medicine

This translational review highlighted the possible druggability of NGF-$TrkA^{NGF}$-$TrkA^{pro\text{-}NGF}$, BDNF-$TrkB^{BDNF}$, and NT3-$TrkC^{NT-3}$ through agonistic or antagonistic trackins for therapy for different pathologies (Table 4). This may contribute to the theoretical hypothesis of an innovative therapeutic frame for further translational investigations dealing with trackins.

Table 4. Trackins and therapy for different diseases; see [3,4,6,23,27–32,57–59,62–64,78,79,85]. * T2/3DM, type 2/3 diabetes mellitus.

Agonists	Antagonists
TrkANGF, TrkApro-NGF, TrkBBDNF, TrkCNT−3	TrkANGF
Cardiometabolic diseases	**Cancers**
Atherosclerosis, hypertension	Prostate, Breast
Obesity, T2DM *, metabolic syndrome	Brain, Pancreas, Lung
Atrial fibrillation	
Diabetic erectile dysfunction	
Cardiovascular diseases	
Arrhythmogenic right ventricular dysplasia	
Sudden cardiac death	
Neurometabolic diseases	
Alzheimer's disease (T3DM) *	**Pain**
Parkinson's disease	**Pruritus**
Multiple sclerosis	
Wounds	
Skin, cornea, bone, axon	

Let us remember that the plasma membrane contains microdomains termed lipid rafts (LRs, existing as caveolae) that are enriched in lipids, such as glycosphingolipids, gangliosides, and cholesterol [86]; LRs are scaffolds for many receptors. Much evidence indicates that the functions of LRs depend upon the interactions with the cytoskeletal microtubules (MT) and MT-associated motor proteins [87]. NGF enhances the interaction between TrkA and MT at lipid rafts controlling different cellular responses including axonal growth [87]. These data suggest the existence of an *intriguing quartet* consisting of NGF-Trk^{NGF}-MT-LR. In the brain, pro-NGF is the only detectable form of NGF; thus, the dysregulation of pro-NGF and/or its $TrkA^{pro\text{-}NGF}$ receptor in the brain could be implicated in age-related memory loss, including AD [87]. Further, the current data suggest that an increase in reactive oxygen species (ROS) and reactive nitrogen species (RNS) reduces the expression of the $TrkA^{pro\text{-}NGF}$ receptor; additionally, the dysfunction of the MT motors kinesin and dynein may lead to disruptions to the $TrkA^{pro\text{-}NGF}$ receptor's downstream survival signaling [88]. Conventional thinking immediately proposes antioxidant treatments as beneficial

in restoring pro-NGF signaling and reducing brain neurodegeneration and related deficits in cognitive function. Since ROS-RNS also interferes with the abovementioned *intriguing quartet* [88], we wonder whether the murburn concept of the biology of oxygen [89–91] could explain such an association between Trk, ROS, RNS, MT, and AD.

Existing limits to Trk-targeting drug development include several critical tasks. One main issue is achieving a high specificity for Trk receptors without distressing similar kinases, leading to off-target results and unsolicited side effects. Furthermore, the progress of resistance mechanisms in the disease through mutations or unusual signaling pathways, obscures the long-term efficiency of these drugs. There are pharmacokinetic obstacles too, such as limited bioavailability and impairments in drug delivery to target tissues, restricting their therapeutic potential. Addressing these limits is crucial for advancing Trk-targeting treatments and improving outcomes for people with Trk-driven disorders.

In a nutshell

The concept of trackins highlighted herein is a promising step forward, but not the whole journey—however, it promises a reward in future translational research. Since 2016, see [3–5,7,22], we have been "pondering what no one else has yet considered about what everyone observes", thus introducing the term trackins [4] with respect to the bivalent nature of the druggability of $TrkA^{NGF}$ and $TrkB^{BDNF}$ receptors and, consequently, their stimulation or inhibition by trackins (pharmaceuticals, nutraceuticals, and/or biologicals), showing the relevance of this subject to therapies for the different diseases discussed in the present short review.

Doubtless, we remember René Descartes' idea that "*de omnibus dubitare, vel dubitare de ipsa*" (from Latin—"everything must be doubted").

5. Addendum

Human love of knowledge leads to the wish to "see inside" the body of organisms. Initially, this was achieved by Aristotle's biology, the first in the history of science, which included five major processes:

1. A metabolic process, whereby animals take in matter, change its qualities, and distribute these to use to grow, live, and reproduce.
2. Temperature regulation, whereby animals maintain a steady state, which progressively fails in old age.
3. An information-processing model, whereby animals receive sensory information and use it to drive movements of the limbs.
4. The process of inheritance.
5. The processes of embryonic development and spontaneous generation

These five processes formed what Aristotle (384–322 BC) called *the soul*, as illustrated in Figure 3:

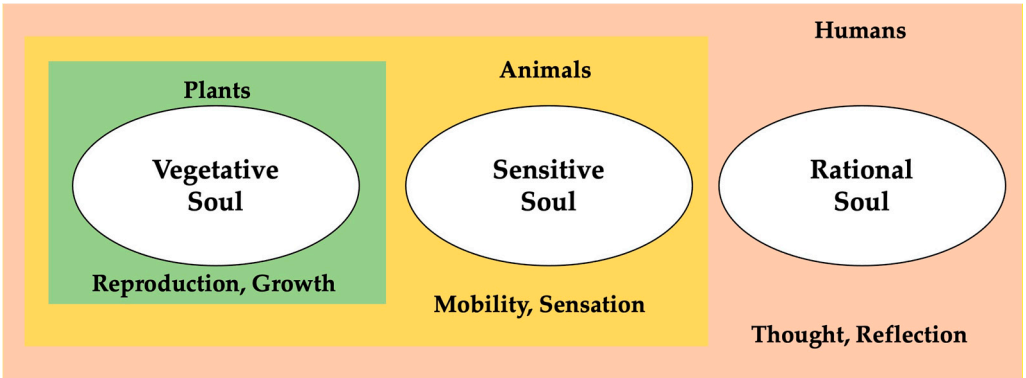

Figure 3. Structure of the soul of plants, animals, and humans. In this vision, humans are unique in having all three types of souls symbiotically. Here, it is reasonable to quote Socrates—"Man is a soul that serves his body"—as a first conceptual step to envisage the soul-and-body interaction [92].

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Conflicts of Interest: The authors declare no conflicts of interest.

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