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Perspective

THERAGNOSTICS OF TRK-TARGETING AGENTS (TRACKINS): A CHALLENGE THAT PROMISES REWARD

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Therminologically, theragnostics combines therapeutics and diagnostics. Life at cellular and molecular level is a binary event (e.g., phosphorylation-dephosphorylation of proteins, methylation-demethylations of DNA and acetylation-deacetylation of histones) aimed at the maintenance of a sanogenic phenotype of the homeostasis. Herein, we focus on the neurotrophins with metabotrophic or pathogenic potentials, particularly nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3) and their receptors Trk (**t**yrosine/tropomyosin **r**eceptor **k**inase; pronounced "track"). Accordingly, the term *trackins* was introduced which stands for Trk-targeting agents influencing agonistically or antagonistically the activity of $TrkA^{NGF}$, $TrkB^{BDNF}$, and $TrkC^{NT-3}$ receptor. We argue that multiple diseases may be trackins curable, for instance: (i) agonistic trackins may have therapeutic potentials for cardiometabolic diseases (e.g., atherosclerosis, obesity, T2DM, and metabolic syndrome) and for neurometabolic diseases (e.g., Alzheimer's disease/T3DM), whereas (ii) antagonistic trackins may be drugs for prostate, breast, gastric, pancreatic and colon cancers, also for pain, and eye, skin and male genitourinary track diseases. Moreover, $TrkA^{NGF}$, $TrkB^{BDNF}$ and $TrkC^{NT-3}$ receptor may be promising biomarkers for diagnosis and prognosis of these diseases. Altogether, the presented data may be a challenge that promises reward requiring a further pursuit. ***Biomed Rev* 2022; 33: 53-60**

Keywords: theragnostics, Trk-targeting agents (trackins), NGF, BDNF, NT-3, cardiometabolic diseases, cancer, Alzheimer's disease

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INTRODUCTION

Life at cellular and molecular level is a binary event (e.g., phosphorylation-dephosphorylation, methylation-demethylations, acetylation-deacetylation of proteins *via* post-translational/post-transcriptional modifications) aimed at the maintenance of a sanogenic phenotype of the homeostasis. Human cells contain more than 500 protein kinases and nearly 200 protein phospatases acting on thousands of proteins including cell growth factors.

The past decade has witnessed remarkable progress in understanding the intricate biology of multiple diseases and providing patients with access to promising therapies. Growth factor receptor tyrosine kinases (GFR-TK) antagonists or agonists being among them. GFR-TK are transmembrane proteins that are involved in cell growth, survival, differentiation, metabolism and various types of apoptosis. More than 60 GFR-TKs has been identified in human inludings for neurotrophins, insulin, EGF, PDGF, FGF, and HGF.

REVERSIBLE COVALENT MODIFICATION (RCM)

Protein interactions are strictly controlled. Much progress has now been made in identifying proteins that attach, recognize, and remove different post-translational/post-transcriptional modifications, and our understanding of these mechanisms has led to the development of novel therapeutics, such as cancer therapies that target protein kinases and histone deacetylases.

Reversible phosphorylation of proteins is abundant in eukaryotic organisms. It is know that one third of all human proteins are phosphorylated at any point in time, with 230,000 unique phosphorylation sites existing in human. Thus, phosphorylation is a universal regulatory mechanism that affects a large portion of proteins.

Phosphorylation-dephosphorylation as well as other RCMs are examples of the binary nature of biological life. The phosphorylation of serine, threonine or tyrosine groups of proteins is the most frequent – it is performed by protein kinases, whereas protein phosphatases cause dephosphorylation. This simple modification alters their functions in many ways, switching their activities on and off. These fundamental findings initiated research field that today is one of the most active and wide ranging. Accordingly, the 1992 Nobel Prize in Physiology or Medicine was awarded to Edmond Fischer and Edwin Krebs for their discoveries concerning "reversible protein phosphorylation as a biological regulatory mechanism".

Edmond Fischer (1920-2021) saw his discovery being applied as drugs that have saved millions of lives – an exciting fact of SOS (state-of-the-science) achievements. The mutation or overproduction of kinases and phosphatases can cause cancer and other diseases. For instance, Imatinib, the first kinase-inhibiting drug, transformed chronic myeloid leukaemia from a rapidly fatal disease to a manageable condition soon after it entered clinical trials in 1998. Protein kinases have since become the pharmaceutical industry's most popular target of drugs. Over 70 kinase-inhibiting drugs have already been approved, improving therapy of many types of cancer; also see (1).

The phosphorylation-dephosphorylation of proteins means covalent attachment-detachment of one or several phosphate groups to or from the protein (Fig. 1).

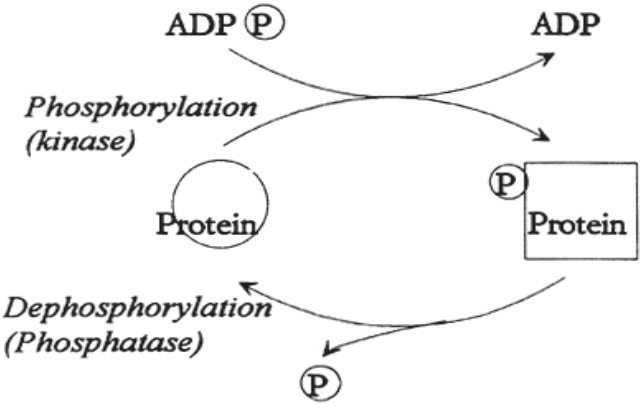

Figure 1. *Reversible protein phosphorylation. A protein kinase moves a phosphate group (P) from ADP (ADP(P)) to the protein, and the biological properties of the protein are thereby altered. There is also a protein phosphatase that removes the phosphate group, a reaction called dephosphorylation. The amount of phosphate that is associated with the protein is thus determined by the relative activities of both the kinase and the phosphatase. This constitutes the basis for the designation of "reversible protein phosphorylation".* **From:** The Nobel Assembly at Karolinska Institute's Press Release. 1972.

ON THE TRUCK: TRACKINS (TRK-TARGETING AGENTS)

In the past 20 years we have been focusing on the neurotrophins, particularly nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and neurotrohin-3 (NT-3) and their Trk (**t**yrosine/**t**ropomyosin **r**eceptor **k**inase; pronounced "track") receptrors (Table 1, Fig. 2). Accordingly, we have introduced the terms *receptozymes* for Trk receptrors, and *trackins* for Trk-targeting agents that influence positively

(agonistically) or negatively (antagonistically) the activity of all GFR-TK including $TrkA^{NGF}$, $TrkB^{BDNF}$ and $TrkC^{NT-3}$. We argue that *trackins* may have therapeutic potentials for multiple diseases, thus these may be considered trackins curable diseases (Tables 2-4).

Table 1. *Trk receptors for neurotrophins**

$TrkA^{NGF}$ (Trk for NGF)
$TrkB^{BDNF}$ (Trk for BDNF) Pro-NGF and pro-BDNF receptors
$TrkB^{NT3}$ (Trk for NT-3)
$TrkC^{NT4/5}$ (Trk for NT-4/5)
$p75^{NTR}$ (p75 pan-neurotrophin receptor)

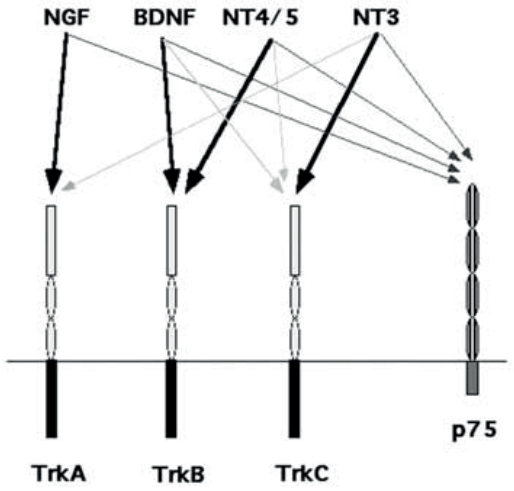

Figure 2. *Neurotrophins and their Trk receptors*. ***From:*** *(2)*

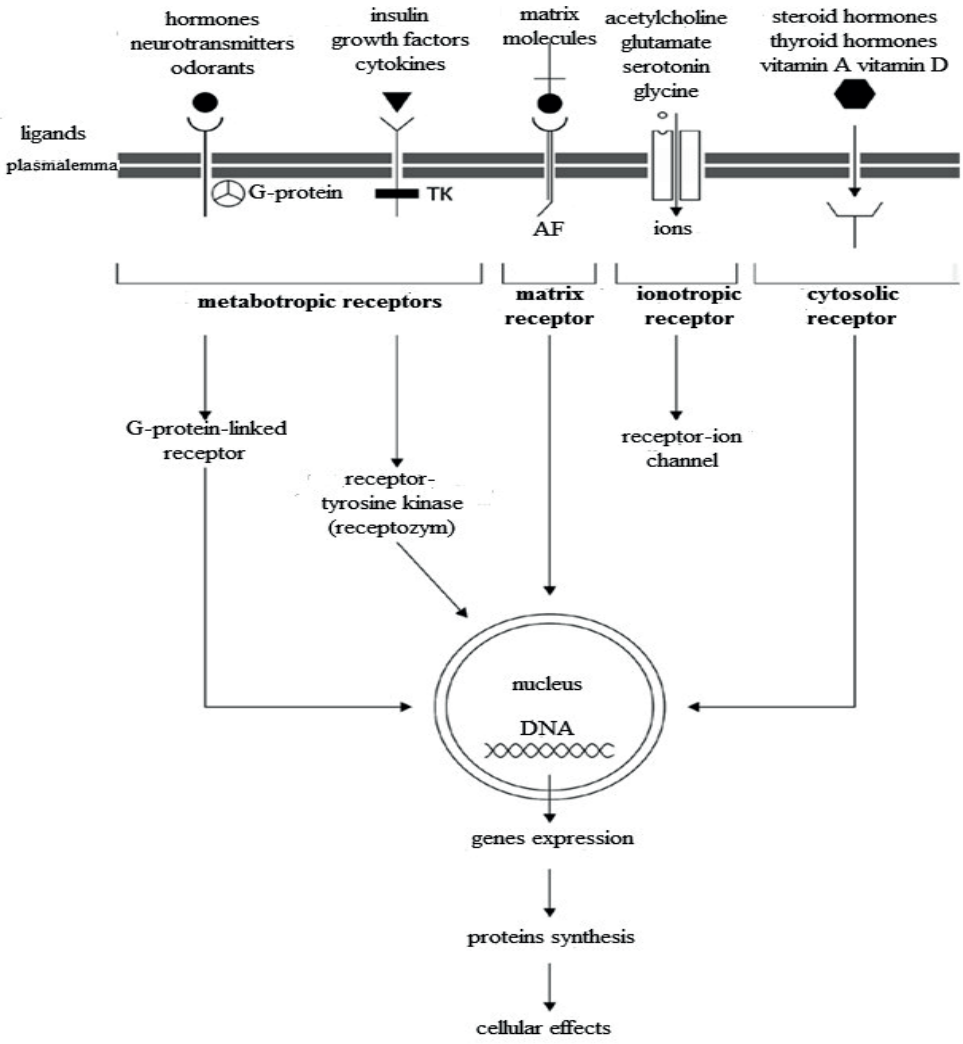

Figure 3. *Schematic illustration of ligand-receptor interactions*. ***From:*** *Chaldakov GN. Principles of Cell Biology. 2021. BioMedES Ltd., Aberdeen, United Kingdom*

Table 2. *Selected list of cardiometabolic diseases*

Atherosclerosis, Hypertension, Acute coronary syndromes (Coronary heart disease)
Congestive heart failure, Atrial fibrillation, Arrythmogenic right ventricular dysplasia
Stroke (ischemic and hemorrhagic), Ischemic non-occlusive coronary artery
Obesity and the related comorbid disorders: • Type 2 diabetes mellitus - Diabetic neuropathy - Diabetic retinopathy - Diabetic erectile dysfunction - Diabetic nephropathy • Metabolic syndrome, Metabolic-cognitive syndrome • Type 3 diabetes mellitus (Alzheimer's disease)

Table 3. *Potential role of NGF and BDNF in the pathogenesis and therapy of diseases (3)*

Neurological diseases	Alzheimer's disease, Mild cognitive impairment, Huntington's disease, Parkinson's disease, Human immunodeficiency virus-associated dementia, Amyothrophic lateral sclerosis, Multiple sclerosis, Epilepsy, Down syndrome, WAGRO syndrome (Wilms tumor, aniridia, mental retardation, genitourinary anomalies, obesity), Cluster headache, Diabetic neuropathy, Diabetic retinopathy, Diabetic erectile dysfunction
Psychiatric diseases	Depression, Schizophrenia, Eating disorders (Anorexia nervosa, Bulimia nervosa), Pervasive developmental disorders (Autism, Rett syndrome, Fragile X syndrome)
Cardiometabolic diseases	Atherosclerosis, Hypertension, Obesity, Type 2 diabetes mellitus, Metabolic syndrome, Heart failure, Myocardial infarction, Sudden cardiac death in diabetes mellitus (silent myocardial ischemia in diabetes mellitus), Kawasaki disease
Ocular diseases	Glaucoma, Retinitis pigmentosa, Diabetic retinopathy, Peripheral ulcerative keratopathy, Dry eye
Skin diseases	Diabetic wounds, Pressure ulcers, Chronic vasculitic ulcers
Malignant diseases	Prostate cancer, Breast cancer, Melanoma, Brain tumors
Urinary system diseases	Overactive bladder syndrome, Benign prostatic hyperplasia
Chronic pain-associated disorders	Osteoarthritis, Low back or spinal injuries, Cancer, Urological chronic pelvic pain syndromes

Table 4. *Effects of NGF and BDNF*

Physiological	**Pathogenic**
Neurotrophic	Oncotrophic (cancerogenic)
Immunotrophic	Nociceptive*
Metabotrophic	Arrhythmogenic
Psychotrophic	Angiogenic
Cognitogenic	Anti-apoptotic

*Stimulation of pain receptors (nociceptors) located at nerve endings in the skin, periostium, blood vessels and internal organs. The envelopes of the brain and its blood vessels as well as the liver capsule also have nociceptors (4).

Table 5. Selective list of anticancer trackins that inhibit Trk рецептори* (5–11)

$TrkA^{NGF}$ receptor antagonists - CEP-701 (Lestaurtinib)* - prostate cancer, pancreatic cancer, acute myeloid leukemia
Epidermal growth factor (EGF) receptors antagonists (Lapatinib, Erlotinib, Cetuximab, Gefitinib) - lung cancer and colon cancer; Herceptin (antibodies) - breast cancer
Platelet-derived growth factor receptor (PDGF) receptor antagonists (Imatinib) - leukemias and other tumors

*CEP-701 (Lestaurtinib) is the chemical substance indolocarbazole that inhibits $TrkA^{NGF}$ receptors. CEP-701 is the trademark of Cephalon Inc., West Chester, PA, USA.

Of note: (i) obesity correlates positively with the progression of prostate cancer and (ii) adipose tissue cells secrete NGF and BDNF (24), (iii) adipocytes located near cancer cells (cancer-associated adipocytes) are synergistically involved in the process of cancerogenesis (25), and (iv) immunohistochemical expression of NGF and BDNF and their $TrkA^{NGF}$, $TrkB^{BDNF}$ и $p75^{NTR}$ receptors both in periprostatic adipose tissue and prostate parenchyma was documented (26).

Another "danger" comes from the hypothesis of NGF-induced increase in sympathetic innervation of the myocardium, suggesting an arrhythmogenic action of this neurotrophin in arrhythmogenic right ventricular dysplasia (ARVD). This is a genetic form of cardiomyopathy, which is characterized histologically by the replacement of degenerated cardiomyocytes with adipose tissue. In the same stream, (i) adipose invasion in the right myocardium is the most significant histological finding in ARVD, (ii) NGF has an arrhythogenic effect associated with sudden cardiac death (27), and (iii) adipose tissue secretes NGF and BDNF, the immunohistochemical

Table 6. Examples of trackins that inhibit Trk receptors, and monoclonal antibodies for cancer therapy approved by USA Food and Drug Administration (12–23)

Small Molecule	Target	Disease	Approval Year
Imatinib (Gleevec)	PDGFR, KIT, Abl, Arg	SML, GIST	2001
Gefitinib (Iressa)	EGFR	Esophageal cancer, Glioma	2003
Erlotinib (Tarceva)	EGFR	Esophageal cancer, Glioma	2004
Sorafenib (Nexavar)	Raf, VEGFR, PDGFR, Flt3, KIT	Renal cell carcinoma	2005
Sunitinib (Sutent)	KIT, VEGFR, PDGFR, Flt3	Renal cell carcinoma, GIST, Endocrine pancreatic cancer	2006
Desatinib (Sprycel)	Abl, Arg, KIT, PDGFR, Src	Gleevec-resistant CML	2007
Nilotinib (Tasigna)	Abl, Arg, KIT, PDGFR	Gleevec-resistant CML	2007
Lapatinib (Tykerb)	EGFR, ErbB2	Mammary carcinoma	2007
Trastuzumab (Herceptin)	rbB2	Mammary carcinoma	2008
Cetuximab (Erbitux)	GFR	Colorectal cancer, Head and neck cancer	2004
Bevacizumab (Avastin)	EGF	Lung cancer, Colorectal cancer	2004
Panitumumab (Vectibix)	GFR	Colorectal cancer	2006

expression of NGF, BDNF and NT-3 and their respective TrkA, TrkB and TrkC receptors in myocardial and adipose tissue in eight cases of ARVD histologically proven on autopsy was studied. The results demonstrated that these tissues expressed NGF/TrkA^{NGF} and NT-3/TrkC^{NT-3}, suggesting pathogenic (or protective?) mechanisms with probable involvement of these neurotrophins and their receptors in ARVD (28). Despite the evidence of cardioprotective and metabotrophic effects of NGF and BDNF, the possibility of TrkA^{NGF} and TrkC^{NT-3} receptor antagonists to have an anti-arrhythmogenic effect remains to further be investigated.

Noteworthy, transactivation of Trk receptors by G protein-coupled receptor has recently emerged as a novel horizon of neurotrophin actions (29).

Likewise, recent studies demonstrated the therapeutic potentials of NGF in other diseases including ocular and cutaneous diseases (30, 31), whereas TrkA^{NGF} antagonists emerged as novel drugs for pain, prostate and breast cancer, and urinary bladder syndromes (see Table 4-6). Last not least, metformin, a widely prescribed drug for T2DM, may exert neuroprotective effect *via* increasing BDNF level (also see Refs in 3, 32, 33).

CONCLUSION

We argue that the diseases mentioned herein may be trackins curable. Hence, the further challenge is to understand to what extent the signaling of the neurotrophin receprors Trk are interrelated with regards to their neuro-, metabo- and oncotophic (Yang-Yin) potentials.

This may help to construct a conceptually novel therapeutic basis for future studies on *trackins* targeting neurotrophin receptors.

Indeed, "the submerged areas of the NGF iceberg loom very large", Rita Levi-Montalcini stated in her Nobel prize lecture reviewing 35 years of research on NGF (34). And may be rewarded indeed (also see 35-61).

CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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