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Pilot Research Project for the Treatment of Local Advanced Disease, Distant Metastases, in Human Malignant Neoplastic Disease. Deactivation of Nodal Cancer Proteins of Intracellular Signaling Pathways through Individualized "Anti-sense" Polypeptides

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Abstract

The research idea of this therapeutic project aims at the selective deactivation of Key Cancer Proteins (KCPs) of intracellular signaling pathways, responsible for the appearance and spreading of malignancy. This may be accomplished through artificially, biosynthesized "Anti-sense" Polypeptides (ASPs) for the KCPs, individualized for every patient and for the specific type of the malignancy, their synthesis will be based at the tertiary molecular structure of the KCPs. The concentration and tertiary structure of the KCPs inside the Malignant's Cell Cytoplasm (MCC) may be identified by taking biopsy from the tumor and then the tertiary structure of the enantiomeric (chiral), ASPs counterparts may be pharmaceutically designed, biosynthesized and selectively delivered to reach the same or higher concentration of KCPs in the MCC. The latter may be accomplished with the new sophisticated pharmaceutical delivery methods such as liposomes, nanomedicine techniques, anthrax toxin derivatives, Spherical Nucleic Acids (SNAs) technology, so as the final concentration of the ASP which reaches inside the MCC to form a racemic mixture (50% D-50% L), or denser towards the one or the other enantiomer (enantiomeric excess). Theoretically, the result of this reaction of the KCPs with the ASPs will be the aggregation of the molecular complexes to insoluble agglomerates or microspheres and consequently deactivation of the specific intracellular pathways responsible for the appearance and spreading of malignancy.

Keywords: "Anti-sense" proteins; Key cancer proteins; Intracellular signaling pathways; Local advanced disease; Distant metastases; Enantiomeric (chiral) polypeptides

Abbreviations:

KCP: Key Cancer Protein; ASP: Anti-sense Polypeptide; MCC: Malignant's Cell Cytoplasm; SNA: Spherical Nucleic Acid; IDP: Intrinsically Disorder Protein.

Introduction

The phenomenon of life and the open thermodynamic systems may be alternatively described from the existence of (i) a distinct separating border from the surrounding environment (ii) specialized structures inside them, which are functioning with some form of energy exchange with the environment and (iii) the medium in which these sophisticated functions are taking place. In the case of the cell, the distinct border is the cell membrane, the medium is the cytoplasm (which mainly consists of water) with all the cellular organelles, such as mitochondria, lysosomes, endoplasmic reticulum, ribosomes and nucleus, where all basic cellular functions for the homeostasis and reproduction are taking place. Regarding current cancer therapy, pharmaceutical targets of the cancer cell are concerning its border (such as cell membrane and the receptors), intracellular structures (DNA, microtubules) and the cellular functions that occur by these (cell cycle, reproduction).

Aim

The research idea of this therapeutic project is focused at the selective deactivation of KCPs intracellular signaling pathways through their stereochemical bounding with individualized, artificially biosynthesized ASPs and deposit of the reaction product as insoluble agglomerates. By applying the principle of complementarity, which in nature creates more thermodynamic stable structures, such as the DNA double helix model described by Professors Watson and Crick [1] and since the time where Professor Louis Pasteur discovered the existence of enantiomers in nature with the separation of tartaric acid in wine and the discovery of racemic mixtures [2], perhaps it is possible, in reverse, to synthesize stereochemically chiral ASPs with the KCPs. The chemical reaction of the KCPs with their "anti-sense enantiomeric counterparts" inside the MCC may form insoluble complexes-micelles inside the MCC, resulting to deactivation of intracellular pathways responsible for the appearance and spreading of malignancy, sustaining proliferative signaling, evading growth suppressors, resistance at the apoptotic signals and their ability for angiogenesis, tissue invasion and metastasis [3].

Method

Theoretically, the "anti-sense" proteins may be individually for every patient and based at hers/his malignancy type artificially synthesized, based on the tertiary molecular structure of the cancer protein/s which is/are overexpressed in the MCC or based on proteins which are only

expressed (for instance fusion oncoproteins) inside the cancer, but not in the normal cell, expressed in various malignant neoplasms, for instance the fusion oncoprotein PAX8-PPARγ highly expressed in the aggressive type Follicular Thyroid Carcinomas (FTC) [4] or the elf4e, highly expressed in Medullary Thyroid Carcinomas (MTC) and in aggressive variants of Papillary Thyroid Carcinomas (PTC) [5]. This/ese protein/s may be firstly identified by taking biopsy from the malignant tissue and afterwards through specialized diagnostic techniques from Pathology, such as immunohistochemistry, staining and molecular techniques, such as crystallography X-ray diffraction technique and Fourier transforms [6] or nuclear magnetic imaging NMR [7], so as a detailed strereochemical analysis of its/theirs tertiary structure/s to take place. The NMR is currently successfully used for the study of various neoplasms, such as colon, breast, oesophagus, cervix in order to classify tumor grade and type. Subsequently, the amino acid sequence of the KCPs should be identified, such as through mass spectrometry technique and then the design of the "anti-sense" counterparts may follow, such as with the assistance of Computational Methods in Drug Discovery [8], or the Iterative Threading Assembly Refinement (I-ASSER) [9] platforms.

When the amino acid sequence of the KCP is identified, the biosynthesis of the anti-sense enantiomer may follow, with the use of the proteomic technology, such as with the Solid Phase Peptide Synthesizer (SPPS) [10]. The synthesis of a regiment of enantiomeric, ASPs, where its/theirs tertiary structure/s to be complementary with the tertiary structure of the overexpressed or selectively expressed proteins at the cytoplasm of the cancer cell, correspondingly with the symmetry seen among D- and L- enantiomers. The complementary/ies enantiomeric/s proteins could be be biosynthesized either with natural L-aminoacids [11], either with the use of D-enantiomeric aminoacids from the expanded genetic code [12], or with combination of both forms (L- and D-amino acids). The synthesis technique of the enantiomeric/s polypeptide/s may be accomplished by following the reverse amino acid sequence of the natural polypeptide/s, fact that warrants further research study. Afterwards, it is essential to determine the concentration of the protein/s target/s inside the malignant cell in order to prepare the regiment of the enantiomeric protein/s at a specific concentration, where to reach 1:1 ratio or more with the protein/s target/s in the MCC and a racemic mixture to be formed. Protein concentration determination inside the MCC can be done through the modified Lowry method [13] or through newer ones such as Protein Quantification Ratioing (PQR) technique, which uses a specific fluorescent reporter and quantifies steady-state protein levels within the cell, These may be done without differences in kinetics of the upstream and downstream proteins, such as folding, maturation and turnover rates to interfere significantly with the accuracy of the measurements [14].

Consequently, with the selective introduction of the therapeutic regiment of the "anti-sense" proteins in the MCC, reaching a 1:1 concentration ratio, a racemic solution of enantiomeric polypeptides (KCPs and ASPs) inside the MCC will be formed, or most probably a solution with an enantiomeric excess of the one or the other racemate. It is known that in a mixture of a pure enantiomer (R or S) and a racemate (RS), the enantiomeric excess (ee) is defined as the percentage (%) excess of the one enantiomer over the racemate based, on the type ee=[R-S]/R+Sx100 [15]. Enantiomers co-crystallize as racemates on the surface, when the ee of the R enantiomer or S enantiomer remain below a critical value, whereas chiral segregation is achieved and globally homochiral surfaces composed of exclusively one enantiomer and these are obtained as the critical ee is exceeded. The heterochiral-homochiral transition is ascribed to the formation of energetically unfavored homochiral molecular dimmers under the control of the majority rules principle at high ee values. At high ee values, the transition from the insoluble racemate conglomerate complex to the soluble pure enantiomer results due to formation of non-thermodynamically favored dimmers of one or other enantiomer (R or S) which cannot be precipitated as insoluble conglomerates [16].

The initial though was the selective crystallization of the malignant cell cytoplasm, "medium", by the selective crystallization of the cancer cells which selectively express or overexpress KCPs, responsible for malignancy appear and spread, but not those which are expressed in the healthy ones. Following this, the conception of "anti-sense" proteins potential therapy has been tried to adjust to already existing therapies for cancer such as the Hyperthermic Intraperitoneal Chemotherapy (HIPEC) [17], without though any concrete scientific data to support it. Upon further research and collaboration with Heleni and Alan, who directed those previously false assumptions to the correct scientific pathway, the current assumption is to produce agglomerates by the chemical bonding of NCPs with their ASP counterparts (Heleni). Also at that time (beginning of the writing of the article) were also to me unknown that cancer DNA modification and editing, such as Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) [18] and the Transcription Activator Like Effector Nucleases (TALENS) [19] are existing therapies (Alan). Thus, the initial theoretic assumption has excluded the genetic editing of the DNA of malignant cancer cell as realistic therapeutic goal and has been moved 2 steps further (translation inhibition and protein aggregation at the post translational level).

Consequently, the research may be firstly redirected at the *in vitro* study of racemic solutions from KCPs from various malignant neoplasms (solids or liquids) with their chiral counterparts, studying the chemical way of aggregation, the temperature, which this may be accomplished and if those factors are compatible with cellular homeostasis *in vivo*. If conglomerate formation is only achieved at thermodynamic conditions not compatible with cellular homeostasis, then as a next step it may studied if the formation of a "supercritical" concentration of a racemate with enantiomeric excess from ASPs could lead to insoluble aggregates-precipitates and deactivation of nodal, for the appear and spread of malignancy, intracellular signaling pathways. The achievement of a "supercritical" saturation of KCPs and their enantiomeric counterparts in a solution closely resembles the MCC or in cancer cell lines *in vitro* and the study of the chemical behavior of the molecules may be done, possible with the method of Supercritical Fluid Chromatography (SFC) [20,21].

In such case, though, the presence of an intermediate binding molecule may be necessary, in order the successfully bonding between KCPs and their chiral polypeptides to occur. This intermediate binding molecule may be attached at the ASP during administration, so as a spherical final insoluble aggregate to form inside the MCC when react with the KCPs. This intermediate molecule may be derived from the category of Intrinsically Disorder Proteins (IDPs) especially from the subcategory of molecular assemblers, Firstly, the Molecular Recognition Elements (MREs) [22] at the polypeptide structure may be first studied and defined with specialized 2D, 3D Virtual Screening techniques (ligand based methods) [23]. The MREs are very important spots, since they represent the molecular places where the first step of protein interactions occur and where molecular docking of IDPs is taking place [22].

The term "enantiomeric" may not be applicable for proteins, as it is used for more simple inorganic chemical substances. The enantiomeric form of a polypeptide, a mirror image one, as it is in the shape of D- and L-, chiral, molecules cannot form a spherical structure, when bringing them in close approximation. The concept of chirality, in the case of a molecule with tertiary structure, as with proteins, would be more correct to refer to a molecule with a reverse tertiary structure in all three dimension (x, y, z axes), which, when it comes in close approximation with the KCP to specifically bound and "lock", such as the key in the keyhole, or such as the enzyme with its substrate, and form an insoluble microsphere. The design should probably care to keep the hydrophobic residual amino acid groups of the ANP at the outer surface of the polypeptide and probably to have a reverse electric charge from the KCP to facilitate their approximation in the MCC (Panos).

Preliminary Experiments

The research efforts may be focused primarily at the *in vitro* study of the aggregation type of racemic solutions from natural cancer proteins from various malignant neoplasms with their synthetic enantiomers, with racemic protein crystallography [24], determining the rigid body degrees of freedom (D) between chiral proteins which need to arrange in a particular manner inside the MCC in order to form an insoluble aggregate. In other words, at how many different points of the protein's tertiary structures may the natural with the chiral proteins to connect in order to form an aggregate and if this may be accomplished in the thermodynamic conditions existing inside the MCCs *in vivo*. The next step may be the test of the thermodynamic stability of those precipitates, agglomerates or micelles inside a solution which closely resembles the MCC and afterwards the MCC itself in cancer cell lines, such as with the techniques of Differential Scanning Fluorimetry (DSF, nanoDSF) [25], Microscale Thermophoresis (MST) [26] (determination of thermodynamic parameters for interactions and monitor of protein folding) , or with the newest Mastersizer and Microflow Imaging (for molecules <28 μm) platforms. With the latter platforms, it is possible to study the aspect ratio of the molecular complexes, meaning the ratio of the depth with the width of the image of the particle, analyzed at the platform. Based on their aspect ratio, the molecular complexes may be divided as fines, microspheres and agglomerates. The formation of microspheres may carry the most favorable thermodynamic form after reaction of the KCPs with their "anti-sense" enantiomers inside the MCC [27]. Also the study may evaluate which specific thermodynamic conditions are needed in order the KCPs and the "anti-sense" proteins to form a stable and insoluble microsphere.

Administration Methods

If the preliminary studies prove the validity of the above theoretic assumptions then phase I trials could commence. A critical question remains the selective delivery of the "anti-sense" proteins inside the MCC in adequate concentration to form the microspheres and deactivating the pathways. The science of nanotechnology-nanomedicine can also contribute to this goal with the specialized delivery methods, such as lipid based nanocarriers (liposomes, stealth liposomes, solid lipid nanoparticles) or with the assistance of smart drug delivery systems, such as nano-sized carriers with characteristics size less than 200 nm and more than 10 nm , with a neutral charge on the surface or a slight negative zeta potential and coat their surface with Polyethylene Glycol (PEG) [28], phospholipid bound nanoparticles, intelligent polymeric nanocarriers, electroactive composite nanogels, drug conjugates (antibody-drug, polymer-drug, polymer-protein), viral, or inorganic nanoparticles. Problems with the introduction of mirror image polypeptides into mammalian cells have been currently surmounted with the use of protective antigens (PA) from *Bacillus anthracis* (anthrax) toxins, attaching the "D-cargo" at the C- terminus of Lethal Factor (LF) domain of the toxin [29]. Another new, sophisticated method, the SNA technology could also offer a solution to the problem of selective delivery. Instead of nucleic acids, at the outer surface of the nanoparticles the individualized ASPs could be bounded, which with their introduction in the MCC, they will be detached from the nanoparticle core and subsequently react with the KCPs, providing a potential new method of individualized treatment [30]. Every other scientific method or proposal may be suggested from scientific committees from universities throughout the world, pharmaceutical companies or fellow scientists of the relevant fields or anyone who are more relevant from the writer and can contribute to the implementation of the idea of "anti-sense" proteins for the treatment of patients with malignant neoplastic disease, which may bring our scientific communities and our nations more close with this common goal.

Applications-Indications

In patients with local advanced (stage III) or generalized metastatic disease (stage IV) in one or multiple organs or in patients with recurrence, when all current anti-neoplastic treatment (medical or surgical) cannot offer any definitive treatment.

Arguments in Favor of the Particular Research Idea

The therapeutic rational of complementarity have been first observed at the post-transcriptional modification of the ompF gene [31] and been already successfully applied with the anti-sense nucleotides (mRNAs) treatment, preventing the translation of specific genes in cancer, such as the cytoprotective chaperone protein, clusterin, in advanced cancer such prostatic, breast, transitional renal cell, non-small cell lung [32], where clinical trials are ongoing. An off-target effect which may be also observed in ASP treatment, correspondingly with the anti-sense RNA treatment, may also eliminated with strategies, such as concentration optimization with SMART "pooling" technique, bioinformatics and modifications of the ASP to resist in protease degradation [33] (Reviewer #2). Also, mirror image polypeptides are not recognized by nature's proteases, are less susceptible to degradation and have also low immunogenic response [34]. If the rational of cancer therapy through ASPs proves to be correct, then perhaps in the future, "libraries" of anti-sense proteins may exist for every malignancy type and only minor adjustments in their polypeptide structure may be done individually for every patient. This may be accomplished with platforms such as the existing Smart Re-profiling platform [35], according the structural analysis of the individualized KCPs, after biopsied the malignant tumor, as it was presented in the article.

Bioethics

Nowadays, with the great evolution of the technology and the scientific methods, as well as the therapeutic possibilities and perspectives that may arise, pose once more as crucial need the redefinition of the limitations of the medical therapeutics and the interventions in patients. It is very important to realize that It is very

important to realize that therapeutic intervention is futile and according to the theories of hedonism and desire-satisfaction, described in the literature for a person's fare well, every possible effort should be made from all health care providers, according to their specialty, to insure patients with terminal illness with adequate pain relief, rehabilitation and sufficient physical and psychological support for them and their families. The clinician must also be aware of their patient's desires regarding the course of their illness and must also be willing to fulfill them, having also in mind the objective list, which means that there are good interventions for the patients, even though themselves are incapable to recognize them and from this point of view the clinicians should always care for the best interest of their patients. Currently, there has also been a trend towards the balanced patient-centred approach from the classical doctor-centred approach of the medical therapy. It is also very important for the patient to actively participate at the final decision of the therapy recommended by the doctor, who always taking into account the personal needs of every patient which is the autonomy, beneficence, non-maleficence, justice, equitable access, privacy, fiduciary duties and always according to her/his individual social, cultural, national features as well as her/his religious and ideological beliefs.

"A deeper look in ethical theory is needed where it seems that a Kantian prohibition towards using merely as a means will conflict with a consequentialist perspective that favors an impartial maximization of good outcomes" (Chris) [36,37,38].

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References

1. Watson JD, Crick FHC (1953) Molecular Structure of Nucleic Acids a structure for deoxyribose nucleic acid. Nature 171: 737-738.
2. Pasteur Louis (1848) Memory on the relationship which may exist between crystalline form and chemical composition, and on the cause of polarization. Weekly Accounts of the Academy of Sciences (Paris) 26: 535-538.
3. Hanahan D, Weinberg RA (2011) Hallmarks of Cancer: the next generation. Cell 144: 646-674.
4. Raman P, Koenig RJ (2014) PAX8-PPARγ fusion protein in thyroid carcinoma. Nat Rev Endocrinol 10: 616-623.
5. Kouvaraki MA, Liakou C, Paraschi A, Dimas KD, Patsouris E, et al. (2011) Activation of mTOR signaling in medullary and aggressive thyroid carcinomas. Surgery 150: 1258-1265.
6. Phillips T (2017) X-Ray Crystallography and the Fourier Transform. Stony Brook University New York.
7. Shah N, Sattar A, Benanti M, Holander S, Cheuck L (2006) Magnetic resonance spectroscopy as an imaging tool for cancer: a review of the literature, The Journal of the American Osteopathic Association 106: 23-27.
8. Sliwoski G, Kothiwale S, Meiler J, Lowe EW, Eric LB (2014). Computational Methods in Drug Discovery. Pharmacol Rev 66: 334-395.
9. Yang J, Yan R, Roy A, Xu D, Poisson J, et al. (2015) The I-TASSER Suite: protein structure and function prediction, Nat. Methods 12: 7-8.
10. Merrifield RB (1963) Solid Phase Peptide Synthesis. I. The Synthesis of a Tetrapeptide. J Am Chem Soc 85: 2149-2154.
11. Hylton RK, Tizzard GJ, Threlfall TL, Ellis AL, Coles SJ, et al. (2015) Are the crystal structures of enantiopure and racemic mandelic acids determined by kinetics or thermodynamics. J Am Chem So 137: 11095-11104.
12. Liu CC, Schultz PG (2010) Adding new chemistries to the genetic code. Annual Review of Biochemistry 79: 413-444.
13. Thermo Scientific Pierce Protein Assay Technical Handbook Version 2: 30-32.
14. Chiu-An L, Kays I, Emran F, Lin TJ, Cvetkovska V, et al. (2015) Quantification of protein Levels in Single Living Cells. Cell Reports 13: 2634-2644.
15. Ernest EL, Samuel WH (2008)Stereochemistry of Organic Compounds 1197-1198.
16. Li SY, Chen T, Wang T, Sun B , Wang D, et al. (2016) Enantiomeric Excess- Tuned 2D Structural Transition: From Heterochiral to Homochiral Supramolecular Assemblies. Langmuir 32: 6830-6835.
17. Sugarbaker PH (2017) Intra-abdominal manifestations of pleural mesothelioma. Ann Transl Med 5: 231.
18. Ishino Y, Shinagawa H, Makino K, Amemura M, Nakata A (1987) Nucleotide Sequence of the iαρ Gene, Responsible for Alkaline Phosphatase Isozyme Conversion in Escherichia coli, and Identification of the Gene Product. J. Bacteriol 169: 5429-5433.
19. Miller JC, Tan S, Qiao G, Barlow KA, Wang J, et al. (2011) A TALE nuclease architecture for efficient genome editing. Nature Biotechnology. 29: 143-148.
20. White C, Burnett J (2005) Integration of supercritical fluid chromatography into drug discovery as a routine support tool: II. Investigation and evaluation of supercritical fluid chromatography for achiral batch purification. J Chromatogr A 1074: 175-185.
21. Gopaliya P, Kamble PR, Kamble R, Chauhan CS (2014) A Review Article on Supercritical Fluid Chromatography. International Journal of Pharma Research & Review 3: 59-66.
22. He B, Wang K, Liu Y, Xue B, Uversky VN, et al. (2009) Predicting Intrinsic Disorder in Proteins: An Overview. Cell Research 19: 929-949.
23. Rester U (2008) From virtuality to reality - Virtual screening in lead discovery and lead optimization: a medicinal chemistry perspective. Curr Opin Drug Discov Devel 11: 559-568.
24. Yeates TO, Kent SB (2012) Racemic protein crystallography. Annu. Rev Biophys 41: 41-61.
25. Frank NH, Helena B, Masoud V (2007) The use of differential scanning fluorimetry to detect ligand interactions that promote protein stability. Nat Protoc 2: 2212-2221.
26. Willemsen MJ, Andre T, Wanner R, Roth HM, Duhr S, et al. (2014) MicroScale Thermophoresis: Interaction analysis and beyond. Journal of Molecular Structure 1077: 101-113.
27. Van Beers M, Merrifield C, Buguliskis JS (2017) Micro-Flow Imaging as a Tool for Pharmaceutical Particle Analysis. GEN Webinar Presentation, 11 July 2017.
28. Yu B, Tai HC, XUE W, Lee LJ, Lee RJ (2010) Receptor-targeted nanocarriers for therapeutic delivery to cancer. Molecular Membrane Biology 27: 286-298.
29. Rabideau AE, Liao X, Pentelute BL (2015) Delivery of mirror image polypeptides into cells. The Royal Society of Chemistry. Chem. Sci 6: 648-653.
30. Jensen SA, Day ES, Ko CH, Hurley LA, Luciano JP, et al. (2013) Spherical Nucleic Acid Nanoparticle Conjugates as an RNAi-Based Therapy for Glioblastoma. Sci Transl Med 5: 152.
31. Mizuno T, Chou MY, Inouye M (1970) A unique mechanism regulating gene expression: Translational inhibition by a complementary RNA transcript (micRNA). Proc Natl Acad Sci 81: 1966-1970.
32. Zoubeidi A, Chi K, Gleave M (2010) Targeting the Cytoprotective Chaperone, Clusterin, for treatment of Advanced Cancer. Clin Cancer Res 16: 1088.
33. Dharmacon. Off-target effects: Disturbing the silence of RNA interference (RNAi).

34. Dintzis HM, Symer DE, Dintzis RZ, Zawadzke LE, Berg JM (1993) A comparison of the immunogenicity of a pair of enantiomeric proteins. Proteins Struct Funct Genet 16: 306-308.

35. Scoffin Robert -Source: Re-Pharm .com www.nature.com/biopharmmadealmakers.

36. Koch PM, Lazaridis C (2017) What does it mean for a critically ill patient to fare well? Intensive Care Med Resuscitation versus Donation: Conflict, Priority and Rational Consent. The American Journal of Bioethics 81: 1-2.

37. Bossaert LL, Perkins GD, Askitopoulou H, Raffay VI, Greif R, et al. (2015) The ethics of resuscitation and end-of-life decisions section Collaborators 1 European Resuscitation Council Guidelines for Resuscitation 2015. Resuscitation 95: 302-311.

38. Lazaridis C (2017) Resuscitation versus Donation: Conflict, Priority, and Rational Consent. The American Journal of Bioethics 17: 27-29.

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