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Is there a future for therapeutic peptides to aid, benefit, and treat cancer in adults? A review and commentary

Abstract

This study addresses a topic concerning the use of therapeutic amphipathic antimicrobial-like peptides in the course of treating adult cancer such as breast malignancies. As a peptide example for this report, a naturally occurring pregnancy protein derived peptide was selected to demonstrate its biochemical and biophysical traits, characteristics, and biological activities. This alpha fetoprotein-derived peptide has been termed the "Growth Inhibitory Peptide" (GIP). Henceforth, this report will describe the origin, discovery, significance, and functions of GIP, with studies in both *in vivo* and *in vitro* published papers. Following an initial discussion, the mechanism of cell penetration, and tumor growth/suppression via the cell growth cycle is described. Finally, additional biological safety activities, toxicities, and side effects of GIP as a therapeutic agent are further addressed.

Keywords: Alpha-fetoprotein; DNA repair; Cell cycle; Cyclin-E; Gene instability; Ubiquitins; Breast cancer.

Gerald J Mizejewski*
Wadsworth Center, New York State Department of Health, Biggs Laboratory, USA.

***Corresponding author:** **GJ Mizejewski**
Division of Translational Medicine, Molecular Diagnostics Laboratory, Wadsworth Center, New York State Department of Health, Biggs Laboratory, Empire State Plaza, Albany, NY 12237, USA.
Tel: 518-486-5900, Fax: 518-402-5002;
Email: Gerald.mizejewski@health.ny.gov

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Origin of alpha-fetoprotein polypeptide as a derived source of the growth inhibitory peptide

Background on Alpha-Fetoprotein (AFP)

AFP is a protein produced during pregnancy by the fetal liver, yolk sac, placenta, and the developing gastrointestinal tract [1,2]. This fetal protein plays a crucial role during the progression of fetal growth and development and is present in microgram concentrations in fetal serum, umbilical cord blood, and newborn serum [3]. During pregnancy, AFP is transported via fetal blood across the placenta and passage into maternal serum. AFP levels drop significantly following birth, and AFP in adults is reduced to nanogram/mL concentrations. Finally, elevated AFP levels in adults have further been associated with certain cancers, such as hepatocellular carcinomas and germ cell tumors [4].

Since AFP is a fetal protein, its appearance in adults is retrogressive and present only in incidences concerning cancer. Further research efforts have been reported on the biological activities and functions of AFP beyond its role in fetal development [5]. These further research efforts have explored potential non-fetal roles of AFP, especially its therapeutic role in cancer growth and autoimmune diseases. In late 1980s and early 1990s, research reports revealed that AFP displayed additional biological activities, including biomarker screening for birth defects, potential cancer treatment, pregnancy remissions, and immunosuppressive properties involving maternal autoimmune diseases [6].

Discovery of the Growth Inhibitory Peptide (GIP)

Following studies involving a search for an anti-estrogenic site on the AFP molecule [7,8] Mizejewski et al. identified a

bioactive amino acid sequence stretch on AFP that involved an estrogen (E2) interaction with the AFP molecule. This 34-amino acid peptide fragment, derived from the full-length AFP molecule, exhibited growth-inhibitory properties especially against estrogen-sensitive and non-estrogen sensitive cancers [9,10]. These 34 amino acid peptide segments, termed the Growth Inhibitory Peptide (GIP), was found to suppress estrogen sensitive tumor cell growth and proliferation in both animal models and in cultured human breast cancer cell lines [11]. This discovery eventually opened new vistas for research into AFP-derived peptides as potential therapeutic agents for both E2-sensitive and non-E2 sensitive cancer treatments. Therefore, GIP was known for its ability to inhibit cell growth, particularly in multiple cancer types, both in cell cultures and *in vivo* animal models. Hence, GIP has been proposed as a potential therapeutic agent for a multiple of malignancies, including breast, prostate, and ovarian cancers. Overall, GIP was reported to be a growth-suppressive agent in nine different human tumor types and to further suppress the spread of tumor metastases in animal models [12,13]. Within the realm of oncology therapeutics, GIP may have a future potential to emerge as a cancer targeting and therapeutic agent due to its distinct cell penetrating, amphipathic properties, and antimicrobial-like activities [14,15].

Significance of the GIP discovery

The identification of an AFP-derived peptide has since added to the knowledge and understanding of AFP's multiple physiological roles in the human body; such studies suggest that AFP is not merely a fetal protein but also a molecular source of an intrinsic peptide with potential applications for cancer therapy. The studies of Mizejewski and associates. further contributed to the broader field of biologically active oncofetal derived peptides expressed during human fetal development [15-17].

Effectiveness

In vitro cultured cell proliferation

In studies at the National Cancer Institute, GIP was assayed against 60 different tumor cell culture lines for its effect on cell growth and proliferation [18] (Table 1). GIP was shown to be growth inhibitory against 38 of the 60 tumor cell lines tested. Nine different tumor types were included among those whose growth was inhibited ranging from 45-85%. Tumor cell types further included prostate, melanomas, small cell lung cancers, various carcinomas, and central nervous system cancers. Further studies at a commercial institute for cancer research (Rambough-Goodwin Institiute), employed a cell energy ATP based assay to demonstrate that GIP's effect on tumor cells was cytostatic rather than cytotoxic [19].

In vivo tumor and teratogenicity studies

GIP suppressed growth of human breast cancer MCF-7, an estrogen receptor positive cell culture line expressing glandular breast cancer cells implanted into nude mice [20]. Similarly, GIP was effective against a human ductal breast tumor cell line, GI 101 in SCID mice, which displays metastasizes within test animals to form lung cancer cell foci. GIP suppressed both the lung metastases and the primary implant site of the GI 101 tumor [21]. In a further study using MDA-MB-231 breast tumor cells lacking an estrogen receptor, growth of the primary mass showed marginal growth suppression, and yet lung metastases were considerably reduced [19,20].

In a prior report, breast ascites tumor studies were performed using an *in vivo* mouse model of a transplanted mammary sarcoma tumor (GWI-1) [12,13]. These studies were performed involving over 1,000 individual test mice. This ascites murine tumor is extremely virulent in a nylar mouse strain producing 100% death after 14 days of incubation. GIP, in a dose responsive fashion, suppressed the ascites tumor cell proliferation, resulting in extended life spans of several weeks in the tumor bearing mice. Histo-pathological examinations revealed that treatment with GIP decreased tumor metastatic infiltrates throughout the entire body cavities of the treat mice.

Mechanisms of growth suppression and arrest

Following the initial studies of AFP-derived peptides (GIP), studies were focused toward understanding the mechanisms by which GIP exerted its anti-growth effects. Following the injection and uptake of GIP-34 into the body cavity of mice, GIP was found to enter into the cancer cell cytoplasm following cell membrane penetration. The intra-cytoplasmic presence of the peptide interfered with various signal transduction cascades enroute to intracellular pathways involving the cell growth cycle of the tumor cell involving both cell division and proliferation [22-24]. The mechanism of action of GIP growth arrest has since been established and was reported to involve blockage of the signaling transduction cascades that ultimately resulted in: 1) cell growth cycle S-phase/G2-phase arrest; 2) prevention of cell cycle inhibitor degradation by ubiquitins; 3) protection of p53 from inactivation by phosphorylation; and 4) interaction of ion gated cell channel involvement by various growth factor activators such as estradiol and Epidermal Growth Factor (EGF) [25]. Thus, the overall inhibitory mechanisms of action of GIP-34 are now well known and were reported in light of the cell's differing modes of cell adhesions, attachments, and cell penetration/uptake [12,13]. Further research reports have employed the methodology of an RNA microarray analysis in combination with electrophysiologic measurements of cell membrane electrical conductance and resistance [23] (Table 1). Thus, GIP as a chemotherapeutic adjunct agent, could potentially aid in alleviating the negative side effects of: tamoxifen resistance, uterine cell hyperplasia, blood clotting, herceptin antibody resistance, cardiac (arrest) and arrythmias, and doxorubicin's bystander chemotherapeutic cell toxicity [23].

When both *in vitro* studies (MCF-7 cells) and *in vivo* (mouse uterine) assays were performed using GIP, it was determined that the peptide could specifically and enter into cancer cells and rapidly accumulate within the cytoplasm of the targeted malignant cells. The time course of cell penetration was found to occur within several minutes. Such timing indicates that the uptake of GIP into cells does not occur by means of cell surface receptor endocytosis which takes considerably longer up to 45 minutes [23]. In addition, the mechanism of GIP's targeting and accumulation in tumor cells was further investigated revealing that GIP functions to reduce the tumor cell membrane electrical resistance involving a negative cell surface charge. The addition of GIP into cancer cell can occur within seconds and the timing was consistent with observations made in conjunction with pulse-chase immunocytochemical studies. The phase light microscopical and other observations revealed that GIP enters cells by creating membrane pores and channels *de novo* similar to that of cell penetrating antimicrobial-like peptides using computer (in silica) modeling [15,23,27-29] (Table 1).

Following tumor cell uptake and penetration, accumulated GIP rapidly diffuses throughout the entire cytoplasmic compartment, and eventually concentrates in foci surrounding the perimeter rim of the nuclear membrane; however, GIP does not enter into the nuclear compartment [23]. The perinuclear rim region with the cell is continuous within extensions of the endoplasmic reticulum. With such perinuclear localization of GIP, it is tempting to speculate that a further function of GIP might be to block translational proteins (such as steroid receptors) from entering the nucleus and influencing DNA translation. It can further be speculated that GIP might act to influence gating of the nuclear membrane pores to regualte nuclear receptor entry. It is known that chronic exposure to GIP can arrest pre-dividing cells in the G1 phase of the cell cycle thus preventing S-phase entry [23,25]. Moreover, GIP is also known to accomplish growth arrest by reducing cellular Cyclin E levels and inhibiting degradation of the p27 and p21 cell cycle inhibitor proteins [23].

GIP was also shown to modify several component factors involved in the process of tumor metastasis. As cancer cells break off from the main tumor mass, they become capable of migration. However, GIP is known to blocks the ability of cells to migrate and spread from the main tissue mass and migrate throughout the vascular system [23,30]. For metastasis to occur, cells must streamline their physical shape in order to enter into the blood stream, and GIP can influence cell shape by modification and alteration of the cell's cytoskeletal system [12]. Aggregates or clusters of attached intervascular of platelets are also known to play important roles in the spread of tumors by binding and complexing with tumor cells enroute to their distal migration sites. GIP inhibits platelet aggregation and therefore prevents the adhesion and binding of tumor cells to the intravascular clusters of platelets [13]. When tumor cells circulate and migrate, they home onto distant tissue/organ sites for implantation. These distant tissues must contain a favorable "nesting" environment for the tumor cells to settle into and attach to the extracellular matrices. Migrating tumor cell metastases are drawn to specific tissues by chemokine attractants. Tumor types require specific type of extracellular matrix proteins for such attachments to occur. GIP can inhibit 60-70% of these nesting tissues attachments consisting of various human proteins such as collagen-1, fibrinogen, fibronectin, collagen-IV, thrombospondin, laminin, and vitronectin [13].

Because of the short lengths of amino acids of peptides, GIP is not thought to use existing small cation channels, but rather use larger non-selective ion channels for calcium, magnesium, and manganese reported in LNCaP prostate tumor cells. Such indicated studies that GIP employs and affects components of the large TRP (transient receptor potential, TRP) family of non-selective ion channels. Computer data has shown that portions of the GIP structure share homology with some of the structural components of the TRP cell membrane calcium family channel [32].

Three ways in which GIP-34 could potentially prevent and/or reduce tumor growth

GIP may possibly be capable of benefiting potential cancer patients in three possible treatment modalities. These three modes of treatment can be proposed to occur as follows: 1) if a person has no known sicknesses, GIP could be taken daily as a preventative supplement to block the initial onset of cancer foci growths [31]; 2) if a subject might already have an existing tumor of a reasonable size, the GIP supplement is capable of suppressing further growth of that intrinsic tumor [18]; 3) If a subject requires that a tumor be destroyed by triggering the process of cellular apoptosis (programmed cell death); such a cell calcium-induced death process could be initiated via calcium channel activating factors in which tumor cells could be induced to proceed to a calcium-induced programmed tumor cell death (apoptosis) process as recently reported [32].

Toxicity & safety issues

As discussed above, GIP is a segment or fragment of an alpha-fetoprotein polypeptide (protein) which can be induced to be exposed and circulate during pregnancy [33]. Alpha-fetoprotein itself is an immuno-privileged protein similar to other placental constituent proteins produced during pregnancy; thus, antibodies are not produced against AFP. In addition, past and present studies have not shown any toxicity or immuno-genecity of GIP in multiple animal and human studies during cell culture, pregnancy, and in adult animals. The GIP peptide segment of alpha-fetoprotein is exposed by cell activation which can be induced during pregnancy. In this new form of transformed AFP, GIP has been reported to circulate at high concentrations in mothers who carry a fetus that is defective, distressed, or possesses a birth defect [33]. Animal toxicity studies have also been performed using multiple doses using GIP with no organ damage was ever observed in any of the animal groups studied which numbered approximately 2,000 animals.

Concluding statements

As described above in the present report, an AFP-derived peptide termed GIP, could possibly fulfill the candidate requirements for an amphipathic antimicrobial-like peptide for cancer therapies such as breast cancer. Such peptides have advantages over the heterocyclic hydrocarbon compounds presently in use as pharmaceutical chemotherapeutics. Such hydrocarbon compounds cannot discriminate between normal dividing cells versus cancer dividing cells resulting in highly unfavorable side effects. In contrast, therapeutic peptides possess high target specificity, short half-lives, low immunogenicity, and favorable safety profiles. In addition, peptides can engage with diverse target specificities which can include intracellular and, extracellular effects. It would not be unreasonable to predict that the global use of peptides as cancer therapeutics will continue to show strong and robust growth trajectories among the multiple worldwide pharmaceutical market forecasts.

Table 1: The Growth-suppressive (cytostatic) screening results* of Human AFP derived Growth Inhibitory Peptide (GIP) for multiple types of human tumor cell cultures*. Cells were exposed to the peptide for six days, fixed, and stained with sulforhodamine-β. None of the cells' lines were dependent on estrogen for growth.

Human tissue or origin	Cell line designation	Tumor tissue type	Conc. range (Molar)	% growth inhibition	Growth response degree
Colon	KM-12	AC	10^{-5}-10^{-7}	75	Suppression
	HCC-299	AC	10^{-5}-10^{-7}	80	Suppression
	Colo-205	AC	10^{-5}	10	Slight Suppression
	HCT-116	AC	10^{-5}-10^{-7}	75	Suppression

Ovary	OVCAR-3	AC	10^{-5}-10^{-7}	80	Suppression
	SK-OV-3	AC	10^{-5}-10^{-7}	60	Suppression
	IGROV1	AC	10^{-5}-10^{-7}	75	Suppression
	OVCAR-4	AC	10^{-5}-10^{-7}	85	Suppression
Breast	MCF-7	AC	10^{-5}-10^{-7}	80	Suppression
	MDA-MB-231	AC	10^{-7} only	80	Suppression
	MDA-MB-435	AC	10^{-5}-10^{-7}	70	Suppression
	BT-549	AC	10^{-6}-10^{-7}	25-40	Moderate Suppression
	T-47S	AC	10^{-5}	25	Slight Suppression
Prostate	PC-3	AC	10^{-6}-10^{-7}	80	Suppression
	DU-145	AC	10^{-5}-10^{-7}	90	Suppression
Melanoma	UACC-62	Epithelial	10^{-4}-10^{-7}	80	Suppression
	SK-MeL-28	Squamous	10^{-4}-10^{-7}	35	Mild Suppression
	SK-MeL-5	Squamous	10^{-5}	10	Slight Suppression
	SK-MeL-2	Squamous	10^{-5}-10^{-7}	50-75	Moderate Suppression
	UACC-257	Squamous	10^{-5}-10^{-7}	75-80	Suppression
Liver	HEP62	Hepatoma	10^{-7}	80	Suppression
Kidney	TK-10	Renal CA	10^{-4}-10^{-7}	80	Suppression
	RXF-393	Renal CA	10^{-6}-10^{-7}	45-50	Moderate Suppression
	A498	Renal CA	10^{-4}-10^{-7}	75	Suppression
	ACHN	Renal CA	10^{-7}-10^{-7}	80	Suppression
	CAK-1	Renal CA	10^{-5}-10^{-7}	50-75	Moderate Suppression

Legends: AC: Adenocarcinoma; CA: Carcinoma

*National Cancer Institute Therapeutics Screening Program, Bethesda, MD, used with permission.

Data derived and extracted from Refs 15, 16, 20.

Ref: Mizejewski, GJ (2023). An Alpha-fetoprotein derived peptide suppresses growth in breast cancer and other malignancies: A review and Prospectus. Med. Res. Arch., 11(7): 1-15

Table 2: Global RNA Microarray: Expression of mRNA 716 transcripts were significantly altered after 8 days of treatment with GIP as compared to treatment with the scrambled control peptide. Four hundred thirty (431) transcripts were down regulated, while 286 transcripts were upregulated.

Microarray data: Transcripts displaying 1.0 or larger log fold (log base 2.0) decrease for genes associated with cell division and proliferation processes		
Gene title	**Fold decrease (-)**	**Cell function**
I. Cell cycle regulation		
1. F-Box, WD40, Domain 10 (FBXW10)	-14.9	Mediates P27 degradation process
2. Checkpoint Suppressor-1 (CHES1)	-9.2	S-phase checkpoint factor
3. Cyclin-E**	-4.6	Regulates G-S transition
4. SKP2**	-4.3	Mediates p27 degradation
5. Calpain	-32.5	Cell cycle progression factor
6. CDC20 Cell Division	-4.3	Regulates ubiquitin degradation
II. Ubiquitin-associated proteins		
1. SUMO/Sentrin/SMT3 specific protease (SENP3)	-2.1	Targets ubiquitin degradation complex
2. Ubiquitin specific protease-49 (MGC20741)	-2.1	Ubiquitin enzyme
3. Ubiquitin Ligase Protein Complex (KIAA0804)	-2.1	Enzyme protein degradation complex
III. Apoptosis Associated Proteins		
1. p53-regulated apoptosis-inducing protein 1 (P53AIP1)	-9.8	Mediates apoptosis
2. Epithelial Membrane Protein 1 (EMP1)	-5.6	Promote and includes carcinogenesis
IV. Calcium Associated Proteins		
1. Phospholipase C, epsilon 1 (PLCE1)	-8.0	CDC25-associated enzyme
2. Solute Carrier Family 22 (SLC22A16)	-6.1	Cation transporter protein
3. Dystrophin (DMD)	-6.1	Muscle/ECM connector
4. Cadherin 13 (CDH13)	-4.9	Cellular adhesion factor

**= real time PCR

Apoptosis= programmed cell death; ubiquitin= protein degrading factor; ECM= extracellular matrix.

Table 3: Antimicrobial and Antimicrobial-like Peptides (GIP-34) are listed and compared according to their biochemical and biophysical characteristics, traits, and properties. Note the similarity of their properties.

Characteristics, Traits, Properties	Antimicrobial Peptides (AMP)	AFP-derived Inhibitory Peptide (GIP-34)	References cited
1) Cell membrane penetration effects	Forms transmembrane pores and/or channels, that reduce the cell membrane potential	Disrupts cell membrane and interacts potentially with transmembrane channels	[12,13]
2) Cell method of internalization and/or endocytosis	Transmembrane channel passage, channel receptor endocytosis	Interacts with membrane channels, a non-receptor endocytosis mechanism	[14,15]
3) Cell-specific targeting property	Microbial cell membrane, plasma membrane of vertebrate (mammals), transformed cancer cells	Plasma bilayer cell membrane; in transformed cancer cells, and bacterial membrane	[18,19]
4) Cargo delivery vehicles	Mostly small cargo delivery capability, binds metals, and fuses with peptides and proteins	Transmembrane passage of small ligands, binds metals, and protein/peptide fusions	[20-23]
5) Cell toxicity	Cytostatic and potential cytolytic toxicity	Cytostatic only	[12,22]
6) Amino acid (AA) composition	Largely amphipathic, contains some positive and negative charged AAs and hydrophobic AAs	Amphipathic form containing positive, negatively charged. And hydrophilic and hydrophobic AAs	[20,22]
7) Number of AAs in length	12-50 AAs	8-34 AAs	[21-23]
8) Peptide secondary structure forms	Displays some alpha-helix, beta sheets, and beta hairpin loops	Displays alpha-helix, beta sheets, beta hairpin loops, and disordered structure	[27,28]
9) Examples of peptides in nature and/or synthesized, and fragments from natural proteins	a) Amphibian-15 peptide b) human dermcidin c) human defensins d) cecropins from insects e) magainin and bombisins from amphibians f) indolicidin from cows g) prophenin from pigs h) horseshoe crabs (sea)	a) (C18G) C-terminal domain of Human Platelet Factor IV b) Hybrid Cecropins A & B c) GIP-34 d) GIP-12 e) GIP-14 f) GIP-8	[12,13]

Legends: AFP: Alpha Fetoprotein; AA: Amino Acids

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