Cancer Therapy & Oncology
International Journal
ISSN: 2473-554X

Juniper Publishers
key to the Researchers

Review Article
Volume 32 Issue 3 - July 2026
DOI: 10.19080/CTOIJ.2026.32.556340

Cancer Ther Oncol Int J

A Review and Commentary on the Growth Regulatory Properties of an Antimicrobial Amphipathic Peptide: Could such Peptides be the Next Generation of Anti-Cancer Therapeutic Agents?

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Submission: June 25, 2026; **Published**: July 15, 2026

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Abstract

Human alpha-fetoprotein (HAFP) is a tumor associated fetal protein of 69 KDa mass which comprises three domains of 200 amino acids each. It has been previously reported that a 34 amino acid peptide fragment derived from the third domain of AFP displays both growth inhibitory and immunoregulatory properties. The growth inhibitory property stands in contradiction to the growth enhancing property displayed by the full-length 3-doamin AFP molecule. Although the growth inhibitory peptide (GIP) fragment lies buried within the AFP polypeptide chain, it can be exposed on the full-length AFP protein surface by means of a molecular conformational change. At present, the 34-amino acid fragment has been isolated and purified as free peptide and characterized in multiple biologic activity assays in both in vivo and in vitro. The subject topics covered in the present report discusses the discovery, isolation, purification, and assay developments for the multiple biologic activities displayed by the antimicrobial-like amphipathic growth inhibitory peptide (GIP).

Keywords: Alpha-Fetoprotein; Growth Inhibitory; Pharmacological; Antimicrobial; Amino acid

Abbreviations: HAFP: Human Alpha-Fetoprotein; GIP: Growth Inhibitory Peptide; AFP: Alpha-Fetoprotein; AA: Amino Acid; HPLC: High Pressure Liquid Chromatography; CD: Circular Dichroism; AMP: Anti-Microbial Peptides; AMLP: AMP-Like Peptides; NCI: National Cancer Institute; ECM: Extracellular Matrix; ADP: Adenosine-Diphosphate; GEG: Gly-Glu-Gly; AC: Adenocarcinoma, CA: Carcinoma; CGIP-34: cyclic GIP-34; DOX: Doxorubicin; TAM: Tamoxifen

Introduction

Human Alpha-fetoprotein (AFP) and the Growth Inhibitory Peptide (GIP):

Human alpha-fetoprotein (HAFP) is a tumor-associated oncofetal protein synthesized in fetal liver, yolk sac, and later in adult hepatomas [1-4]. HAFP has a molecular mass of 69 KDa and is largely an alpha-helical protein, comprising three domains of nearly 200 amino acids (AA) each. Interestingly, in its native full-length form, HAFP displays only growth-enhancing properties, regardless of whether the tissue is of fetal or cancer origin. Due to this growth property, HAFP at physiological/pharmacological dose levels have been reported to enhance both fetal and tumor cell growth [5-8]. As an example of an antimicrobial-like peptide, this treatise will utilize a peptide derived from the third domain of the HAFP polypeptide. It has been previously reported that a 34-amino acid (AA) peptide fragment, derived from the third domain of HAFP, can bestow a transient growth suppressive property upon the full-length AFP molecule; this is in contra-distinction to the growth enhancing properties of HAFP [4,9,10]. HAFP in this transient molecular form is referred to as "transformed AFP" [11]. The 34-AA peptide segment has now been isolated and purified as a free peptide from the third domain of HAFP. This domain contains the 34 AA peptide sequence stretch that normally lies buried (concealed) in a molecular cleft within the full-length native HAFP. The isolated and purified 34 AA synthetic peptide has been termed the "Growth Inhibitory Peptide" (GIP). At present, it has been established that the purified GIP is capable of growth suppression in a multitude of human tumors, both in vitro and in vivo [9,11].

The encrypted (buried) GIP segment on HAFP was initially discovered by matching its AA sequence identity and similarity with members of the heat shock protein family (i.e., HSP-70). These proteins are associated with (1) steroid receptor complex binding, and (2) transient protein folding/unfolding in the endoplasmic reticulum [12,13]. Thereafter, it was determined that the burial and exposure of the GIP segment on the HAFP polypeptide represents a folding intermediate stage (i.e., molten globule form) of the entire full-length HAFP protein [14]. This transformed intermediate molecular form of HAFP has been researched and described in detail in human clinical studies [11]. In summation, the intermediate transient (transformed) version of HAFP has been confirmed to be a molten globule molecule, a folding intermediate stage of full-length HAFP described in a multitude of reports [14,19] (Table 1).

In prior publications, it was demonstrated that GIP was both an estrogen-and cytoskeleton-associated peptide capable of cell penetration and uptake followed by a subsequent cytoplasmic perinuclear localization [10]. It was also reported that GIP showed activity at the cell surface plasma membrane where it can influence cellular shape and form, immune agglutination, and cell/platelet aggregation. Since cell shape and form are related to cytoskeletal and microtubule-associated proteins activities, these cell-surface events served to provide further evidence that GIP segments could affect cell spreading, adhesion, and cell attachment events reminiscent of metastasis [12,13,15]. Historically, both native AFP and the derived GIP have been implicated with activities such as erythrocyte agglutination and platelet aggregation, in addition to tumor cell adhesion to extracellular matrix proteins [12,13,14]. For these reasons, the cell aggregation and adherence activities of GIP will be reviewed considering GIPs growth arrest and associated properties in both human and animal cancers.

Peptide synthesis, characterization, and properties of GIP:

GIP together with the peptide controls were synthesized by F-MOC chemistry using an Applied Biosystems 431 A peptide synthesizer (Foster City, CA) and purified on reverse phase high pressure liquid chromatography (HPCL) as previously described [15-19] (Table 2). The biochemical and biophysical assay results revealed a peptide with a molecular mass of 3573 Da determined by electrospray ionization mass spectroscopy [20-23]. The use of far UV circular dichroism (CD) further displayed a negative wave maximum at 201 nm and structurally indicated the presence of β-sheets and turns (45%) and other disordered structures in equal (45%) proportions, while the remaining structures were composed of α-helices [21,22]. Overall, GIP is a peptide largely composed of beta sheets and turns. Both Fourier infrared spectroscopy and GCG computer modeling software further confirmed the presence of a largely β-sheet structure for GIP. Both a linear and a cyclic version of GIP were synthesized, and computer modeling was performed as previously reported; the single-letter amino acid code sequence of GIP, its fragments, and control peptides have been previously described in detail [22,23].

GIP as a Cell-Penetrating, Pore-forming Peptide:

GIP has the capability to serve as a novel cancer therapeutic agent by mimicking the functions of anti-microbial peptides (AMP) [24]. Such peptides have been demonstrated to lyse and destabilize bio-membranes, interact with and form transmembrane channels, engage in modulating host immunity, and act in concert with activities of chemokine, histamines, and angiogenic factors [25]. Serving as an AMP-like peptide, GIP could aid to reducing the onset of drug resistance within cells, and lower costs of expensive anti-cancer therapeutic drugs. AMP peptides, like GIP, can display lengths extending from 10-50 amino acids (AA), contain two or more cationic AAs, comprise a large proportion of hydrophobic AAs, and are rich in anionic AAs [26]. These peptides, like GIP, also contain many dipolar ions (Zwitterions) and belong to the so-called “amphipathic” class of peptides which contain secondary structural features such as 1) alpha-helices, 2) beta strands, 3) beta-hairpin loops, and 4) one or more disulfide bonds [27,28].

The amphipathicity features of such peptides possess the advantage to partition and permeabilize (penetrate) into cell membrane bilayers while forming and/or interacting with transmembrane channels through electrostatic attractions [23]. Following cytoplasmic internalization, the AMP-like peptides (AMLP) such as GIP, can interrupt down-stream cell activities such as a) DNA, RNA, and protein syntheses, b) protein folding, c) signal transduction, d) receptor crosstalk, e) cell membrane reformation, and f) enzymatic interactions [29-31]. Like the cell surface membranes of bacteria, cancer cell membranes display a cell surface net negative electrical charge; this contrasts with normal, non-malignant cells which display a net positive cell surface charge [24,28]. Cancer cell membranes are rich in phospholipids such as phosphatidylglycerol, phosphatidylserine, phosphoglycerol, gangliosides, phosphatidylcholine, and sphingomyelin. In non-malignant normal cells, the phospholipid headgroups within the outermost cell membrane leaflet bilayers are positively charged, while the innermost bilayer leaflets are negatively charged [24].

In contrast, in cell surface membranes of cancer cells, a phospholipid headgroup with a negative charge can flip to the outermost leaflets of the cell surface bilayer membrane (i.e., phosphoglycerol flips with phosphatidylserine) [27,30]. This phospholipid flip results in a cell surface outer leaflet bilayer membrane bearing a net negative charge. The main attractive driving force behind the electrical charge of GIP and the negative charged cancer cell membrane is an electrostatic attraction [31,32]. It is in this electrical attraction that GIP peptides can be specifically targeted to cancer cells rather than homing onto normal non-malignant cells having a positive charge [24]. Thus, unlike

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most cancer chemotherapeutic drugs that target both dividing/proliferating non-cancer and cancer cells indiscriminately, GIP acts to selectively home onto only the cell surface negative charge membranes of cancer cells [31,33]. This specific homing feature alone, allows GIP to avoid the toxic bystander off-target cell damage that can occur in normal non-malignant cells.

Table 1: The Different Alpha-Fetoprotein (AFP) Forms, and Their Function.

Alpha-Fetoprotein Forms	Biological Roles, Activities	References Cited
1. Denatured Intermediate Forms	A secondary structure form lacking a rigid tertiary structure is referred to as a "molten globule" (MGF) form of the protein; the MGF is considered a slightly denatured molecular state	16, 17, 18
2. Conformational Change	Forms of AFP that have undergone a conformational change in their tertiary structure following exposure to hidden occult sites.	19, 20
3. Misfolded Protein Forms	An unfolded form of AFP due to faulty chaperoning by HSP 70, HSP 90, Bip molecules, and HSP 60 during periods of heat shock, oxidative stress; ischemia, and anoxia	16, 21, 22
4. Transformed alpha-fetoprotein (Tr-AFP)	A form of AFP which has undergone a conformational unfolding to expose a hidden growth inhibitory peptide omit segment that suppresses fetal growth defects during pregnancy.	11, 14, 17
5. Synthetic GIP Peptide Segments: A) GIP-A B) GIP-B C) GIP-C	Peptide fragmented segments isolated from AFP include fragments from AFP protein. A segment termed Growth Inhibitory Peptide (GIP) consists of 3 portions, GIP-A (12 AA), GIP-B (14 AA), GIP-C (8 AA), which regulates growth and inhibits cancer growth via cell cycle arrest and redox control.	12, 13, 14

Table 2: 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 Growth Inhibitory Peptide (GIP-34)	References Cited
1) Cell membrane penetration effects	Forms transmembrane pores and/or channels, that reduce the cell membrane potential	Stabilizes 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; 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

Legend: AFP=Alpha fetoprotein, AA=amino acids.

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Table 3: 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	Moderation 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	85	Suppression Moderate Suppression
	RXF-393	Renal CA	10-6-10-7	45-50	Suppression
	A498	Renal CA	10-4-10-7	75	Suppression
	ACHN	Renal CA	10-7-10-7	80	Moderate Suppression
	CAK-1	Renal CA	10-5-10-7	50-75	Moderate Suppression

Legend: AC: Adenocarcinoma, CA: Carcinoma

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

Data derived and extracted from Ref. 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 4: The growth suppressive effect (%) of cyclic GIP-34 is shown at optimal concentrations for multiple breast tumor cells in culture using 10% fetal bovine serum. The peptide results are compared to treatment with doxorubicin (D)X) and tamoxifen (TAM) shown growth suppression at their optimal concentrations. All drugs and peptides were given at a single dose lasting for either 2 days or 7 days.

Tissue of Origin	Breast Cell Line Designation	Growth Suppression (%) and Optimal Conc. (M)			
			CGIP-34	DOX	TAM
Breast	HCC1143	2D	50 (10-8)	100 (10-6)	60 (10-7)
		7D	10-8	ND	ND
Breast	T-47D	2D	10-8	ND	ND
		7D	10-8	87 (10-6)	74 (10-5)

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Breast	BT 483	2D	22 (10-8)	85 (10-6)	71 (10-7)
		7D	39 (10-5)	11 (10-6)	0 (-)
Breast	MCF-7	2D	88 (10-8)	52 (10-6)	60 (10-6)
		7D	10-8	72(10-6)	63 (10-7)
Breast	MDA-MB-157	2D	10-8	91 (10-6)	70 (10-5)
		7D	36 (10-7)	6 (10-5)	0 (-)
Breast	MDA-MB-468	2D	21 (10-8)	100 (10-6)	87 (10-5)
		7D	38 (10-7)	33 (10-5)	0 (-)
Breast	BT 549	2D	50 (10-6)	100 (10-6)	100 (10-5)
		7D	6 (10-7)	10 (10-6)	0 (-)
Breast	ZR75-1	2D	10-8	100 (10-6)	48 (10-5)
		7D	50 (10-6)	ND	ND
Breast	TX-2-28	2D	24 (10-7)	98 (10-6)	69 (10-5)
		7D	10-8	67 (10-6)	80(10-7)
Breast	MCF-10	2D	10-812 (10-7)	98 (10-6)	61 (10-5)
		7D		0 (-)	0 (-)
					97 (10-6)
Soft Tissue	RD	7D	10-8	ND	ND
Bone	TC-71	7D	10-8	ND	ND
Bone	DORA-1	2D	ND	ND	ND

References: See text references # 9, 34, 35, 36

Legend: CGIP-34: cyclic GIP-34; DOX: Doxorubicin; TAM: Tamoxifen.

Table 5: Comparison of % growth/inhibition of the hollow fiber assay of linear GIP-34 versus 12 different tumors of six cell culture cancer types. Inhibition was observed at concentration of 10-5 to 10-7 M. Hollow fiber (HF) in vivo results at day 4 are compared to the in vitro results at day 2 and day 6 of cell culture**.

Tumors used (Type and Number Code)	In vitro cell culture*	In vivo hollow fiber
	2 days	4 days
1. Lung NCI-H23, H 226	5% (10-7)	33% (10-6)
2. Lung MCI-H522, H460	30% (10-7)	33% (10-5)
3. Breast MDA-MB-231	25% (10-7)	16% (10-7)
4. Breast MDA-MB-435	20% (10-6)	30% (10-6)
5. Colon SW260, HCC-299	10% (10-6)	25% (10-6)
6. Colon 205	10% (10-7)	25% (10-6)
7. Melanoma LOX	20% (10-6)	24% (10-5)
8. Melanoma Uacc-62	20% (10-7)	8% (10-6)
9. Ovary Ovcar-3	20% (10-7)	30% (10-6)
10. Ovary Ovcar-4 5	20% (10-6)	42% (10-6)
11. CNS U251	15% (10-7)	26% (10-5)
12. CNS SF-295	25% (10-6)	20% (10-5)

GIP-34, linear 34-mer growth inhibitory peptide; CNS= central nervous system

6-day hollow fiber, data obtained from hollow fibers assays (containing tumor cells) tubes implanted into the body cavity of adult mice for a 6-day treatment with GIP-34 peptide.

*Cell culture assayed at day 2 and at day 6 using the Sulforhodamine stained procedure. Culture fluid contained 5% fetal bovine sera.

**Both the in vitro and the in vivo assays were performed by the National Cancer Institute Drug Screening Program (Bethesda, MD and Frederick, MD). The hollow fiber testing was conducted by Dr. Melinda Hollingshead (Frederick, MD) and the cell culture assays were performed under the direction of Dr. Anthony B. Mauger (Bethesda, MD), National Cancer Institute.

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Table 6: 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 phase
4. SKP2**	-4.3	Mediates p27 degradation
5. Calpain	-32.5	Cell cycle progression factor
6. CDC20 Cell Division	-4.3	Activates ubiquitin degradation
II. Ubiquitin-Associated Proteins		
1. SUMO/Sentrin/SMT3 Specific Protease (SENP3)	-2.1	Lysine targeting ubiquitin degradation complex
2. Ubiquitin Specific Protease-49 (MGC20741)	-2.1	Ubiquitin enzyme
3. Ubiquitin Ligase Protein Complex (KIAA0804)	-2.1	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 carcinogenesis
IV. Calcium Associated Proteins		
1. Phospholipase C, epsilon 1 (PLCE1)	-8	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

Effect of GIP on Cancer Cells Growth:

In Vitro and In Vivo Cancer Cell Culture Lines:

The summary findings on GIP reported by the National Cancer Institute Therapeutic Drug Screening Program (Bethesda, MD) have been previously reported and described [34-37] (Table 3). These results reported in detail the in vitro studies of GIP assayed in cell cultured tumor cell lines representing a vast array of human cancers (9,39,40) to serve as a cytostatic (non-cytotoxic) agent against 38 of 60 cancer cell lines, of which nine different cancer cell types were represented; such tumors included prostate, breast, ovarian, and multiple other cancer type (Table 4) [35,37]. In subsequent reports (Table 4), the effective use of GIP against various breast cancers was also described in studies involving various substrains of breast cancer cells both in vivo and in vitro (Table 4) [37]. In other experiments, the GIP (encapsulated 0.5 µg/day release pellets) also inhibited the in vivo growth of the human GI-101 breast cancer lines which cells are represented as a non-estrogen-dependent, p53-responsive, tamoxifen-resistant ductal cell carcinoma transplanted as xenografts into nude mice [31,32].

In this latter study, time release pellets of GIP were administered for a 60-day duration period, which readily suppressed tumor growth. In a second study employing a 20-day time-release pellet, GIP was found to suppress the in vivo estrogen dependent growth of MCF-7 human breast cancer xenografts in nude mice; this study utilized a pellet release rate of 0.25µg peptide/day [41]. In subsequent cell culture cytostatic assays, GIP suppressed growth by 50-80% in four of five human breast cancer cell lines maintained in non-estrogen supplemented cell culture media (Tables 3 & 4). This latter study notably demonstrated an estrogen-independent mode of growth suppression (60-70%) by utilizing the AMPL-GIP. In a further series of in vivo nude mice xenograft studies, GIP was effective as a growth suppressing agent (70% inhibition) in a GI-101 breast tumor even after withdrawal of peptide release pellets [41,42]. The GI-101 treated animals that had received GIP pellet implants for 60 days, survived for 45 days after removal of the peptide implant.

At 105 days, the mice were sacrificed and the tumor-volumes were recorded as indictors of active growth. When the remaining mice on GIP treatment were compared to sham controls, 3 of 4

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surviving test animals continued to display 40-50% suppressed tumor growth [41]. In subsequent in vivo tumor studies, nude mice were implanted with MDA-MB-231 strain (non-estrogen receptor) breast tumor cells and similarly treated with GIP time-release pellets. These latter tumors displayed a growth suppression of 30-40% in vivo during administration of 60-day GIP implants, like the results of the prior in vitro assays, displaying 30-50% growth suppression [42]. However, histopathological examinations following autopsy at day 105 (after GIP implant depletion) revealed that the tumor-bearing nude mice that received the GIP implants displayed metastases on an average of 1.5 nodules per lung lobe compared to 4.25 nodules per lobes in the lung of control tumor-bearing mice. Thus, GIP was shown to reduce metastasis in the mice by nearly 3-fold. Finally, when mice were implanted with multiple different cell-cultured tumor cells employing an in vivo hollow fiber cancer cell growth assay, tumor growth suppression was found to range from 20% to 45% (Table 5).

As previously shown in published reports, GIP was shown to target to and deliver drug payloads to cancer cells in addition to suppressing cancer growth in multiple cell lines provided by the National Cancer Institute (NCI) (Tables 3 & 4). In these cancer cell lines, GIP was found to arrest cell growth in several different types of cultured cancer cell lines, including breast, prostate, and ovarian cells among others. GIP can further induce the arrest of cytoplasmic cell cycle growth by halting the cell growth cycle at the G1 to S phase, in addition to blocking the degradation of cell cycle inhibitors such as p27 (KIP) and p21(CIP). Finally, a global RNA microarray data was performed using MCF-1 breast cancer cells treated with GIP for 6 days (Table 6). Transcripts displaying 2.0 or larger log fold (log base 2.0) decreases in genes associated with cell division and proliferation processes, ubiquitination, and calcium-associated factors were recorded from Human MCF-7 breast cancer cells in vitro (Table 6). The RNA expression of 716 transcripts was significantly altered in MCF-7 cells after 8 days of treatment with GIP as compared to the same treatment with scrambled control peptides. The expression of 432 RNAs were down regulated, while 286 RNAs were up-regulated both confirmed by real time PCR (see Table 5).

GIP as an Anti-Angiogenesis Factor:

The progressive stages involved in angiogenesis are known to be composed of 4 major events [52]. These events include: A) cell migration, B) cell proliferation, C) cell survival, and D) vessel tube assembly (tubulogenesis) [43-47]. Previous reports had demonstrated that GIP peptides were capable of inhibiting all 4 major events of on-going progressive angiogenesis [12,13]. These events promote angiogenic activities in both normal and cancer cells and tissues. GIP was found capable of inhibiting all four activity stages leading to angiogenesis [12,13,46].

GIP as Cell Adhesion and Cell Shape Modifiers:

Cell adhesion assays

The GIP fragment itself possesses short internal amino acid stretches that have sequence identity with a variety of extracellular matrix (ECM) proteins [47,48]. Therefore, GIP was utilized in cell adhesion studies involving many of the major ECM-associated proteins. Various ECM proteins were adsorbed to the microtiter plate inner well surfaces and screened for their abilities to serve as a substitute for enhanced breast tumor cell adhesion in arrays employed to compare ECM with non-ECM matrix microtiter control plates. All ECM proteins and tumor cells adsorbed to the microtiter inner surface plates showed rates up to 40-60% adsorption [12,13]. The adhesion of in vitro MCF-7 and in vivo 6WI-1 cells either in the presence of peptide or in peptide-free medium were then tested on ECM-coated microtiter plates, using 3µg of soluble GIP/well as a competitive inhibitor [36,40]. GIP was added to the wells immediately after the cells were displaced with reagents and the mixture was then incubated [12,13].

The GIP fragment could inhibit cell adhesion to nearly all the ECM proteins employed in both human MCF-7 and murine 6WI-1 breast tumor cell lines (Figure 6). Inhibition of mouse and human tumor cell adhesion were roughly equivalent on the plates adsorbed with ECM proteins including collagen IV, fibrinogen, fibronectin, and thrombospondin; in comparison, cell adhesion inhibition was only slightly less for laminin, collagen-I, and vitronectin when the two human and murine tumor types were compared [12,13,37]. Cultured human MCF-7 breast cancer cells, in the presence of GIP, displayed substantial inhibition to vitronectin-induced adhesion while mouse tumor cells 6WI-1 were less blocked. In a similar fashion, mouse 6WI-1 cells demonstrated strong peptide inhibition of laminin adhesion, whereas MCF-7 cells failed to adhere to laminin. Overall, the GIP peptide, in the presence of tumor cells, was found to competitively inhibit both MCF-7 and 6WI-1 cell attachment by 40-50% [36,37]. Thus, GIP was found capable of producing various degrees of adhesion inhibitions, dependent on the ECM protein coated on the well of the microtiter plate, and to the tumor cell type involved (human vs mouse-derived) [12,13,42].

Tumor Cell Migration and Spreading on Cover Slips:

The GIP treated, untreated, and ovalbumin control peptide-coated coverslips were placed in individual 24-well microtiter plates for assessment of MCF-7 breast cancer cell spreading and migration [41-43]. Results of the cell spreading/migration studies revealed that the GIP coated surfaces resulted in a substantial inhibition of cell spreading (mitigation) over a wide concentration range, which peaked at 10µg/ml [41,42]. The tumor cells, which were unable to migrate and spread, displayed distorted morphology such as star-shaped configurations, cytoplasmic

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spiking, surface spiny spheres, and extended cytoplasmic processes, in addition to low cell viability [12,13). These data support the findings of the cell adhesion and mitigation studies described above and re-affirm that GIP is implicated in both cell surface activities and in cell-to-ECM interactions; such reactions suggest the presence of an integrin-like involvement with basement membranes, interstitial surfaces, connective tissues, and metastasis (see below). Depending on the integrin protein involved, differing anti-apoptotic effects of cell spreading have been delineated and described [48-51]. Such reports revealed that ECM proteins were involved in cell morphology and cell shape events and were the major factors in determining subsequent cell growth and survival. Furthermore, it was reported in prior studies that GIP had the capability to alter both cell shape and cell form [48]. Thus, it appears that therapeutic intervention at the integrin-ECM interface (on a GIP platform) could provide a possible explanation for the altering of cell signals and receptor crosstalk's responsible for the delicate balance between cell death and cell survival.

Platelet Aggregation (in vitro)

GIP was also assayed for human platelet aggregation through measurement of their degree of light transmission with an aggregometer, using stirred human donated human platelet suspensions in a reaction vessel [52,53]. Following the addition of an agonist, activation of platelet aggregation proceeds forward in a multi-step process. The aggregation process can be divided into two phases: (a) primary aggregation, which is an immediate and reversible process; and (b) secondary aggregation, which is irreversible and associated with the release of thromboxane [52,53]. GIP was initially found capable of inhibiting the platelet shape and form changes in the aggregation response. Platelet shape and form are dictated by the cell bilayer membrane and the internal cytoskeleton, the latter of which are composed of actin/myosin filaments [52,53]. Adenosine-diphosphate (ADP) induces the change in platelet shape through cytoskeletal (mechanical) forces driven by the distribution of certain organelles within the platelet cytoplasm [54].

In a previous study, GIP interaction with the plasma membrane cytoskeleton and microtubule polymerization has been reported in several models, including elements of α-tubulin and actin filaments [51]. The GIP peptide (100-300μg) was further found to inhibit ADP induced platelet aggregation by 90-95%; while at 10μg, GIP inhibition did not occur [12,13]. It was further demonstrated that a sub-fragment 14 AA- midpiece of GIP (GIP-B) (Table 1), displaying a von Willebrand Factor sequence identity, also inhibited ADP-induced aggregation by 80-90% inhibition. Further characterization of the ADP-induced inhibition by GIP included a decrease in surface-expressed CD62 (P-selectin) fluorescent staining of ADP-activated platelets assayed by flow cytometry [13]. When collagen was used as an agonist activator of platelet aggregation, GIP (100μg) was capable of inhibiting (<90%) the collagen-induced secondary aggregation response. When collagen was used as an agonist activator, GIP could inhibit >90% of the total aggregation [54].

Tumor-Induced Platelet Aggregation:

Tumor cell-induced platelet aggregation is a necessary step leading to metastasis, as first described by Gasic in the early 1970s [55]. Tumor cells in the blood vasculature system are frequently observed in complex formation together with platelets, and these two cell-factor associations together with the hypercoagulable state of malignant disease, appears to be essential for successful completion of the metastatic formation process [48,52]. The ability of tumor cells to induce platelet aggregation is widespread among cancers including breast carcinomas and colon cancers. Platelets themselves act to facilitate all of the intermediate steps required for intra-vascular metastasis including tumor cell retention and arrest, subendothelial interaction, and extravasation from a microvascular event. Blockage at these platelet activities could retard or reduce the expansive spread of tumor cell metastasis throughout the body. As noted above, GIP can inhibit tumor cell adhesion to the ECM as well as platelet aggregation, both of which are required for further advancement of the metastatic process.

The Integrin Disruptors: The Disintegrin:

In previous research reports, a wide array of 30-50 AA containing peptides derived from viper and pit viper venoms termed disintegrins, have been shown to disrupt normal integrin function and serve as potent inhibitors of platelets aggregation [54]. A disintegrin motif also constitutes a structural portion of proteins belonging to the ADAM family of metalloproteinase enzymes [56,57-59]. The viper-associated disintegrin-like peptides are hemostasis-disrupting factors that can be readily distinguished from the cobra-like venoms, which act as neurotoxins. Like GIP, some disintegrins can also induce growth suppression in tumors [60]. Most disintegrins contain the triamino acid sequence of RGD (Arg-Gly-Asp) a cell adhesion sequence; other similar sequences are rich in cysteine, and function to block platelet aggregation. Inhibition of aggregation is a result of a steric blockade involving the binding of integrins to different ECM proteins.

In comparison to the above discussion, GIP contains the amino acid triplet sequence of Gly-Glu-Gly (GEG) which is also present in many disintegrins and plays a role in platelet aggregation inhibition [56,57]. Thus GIP, like disintegrins, could represent lead molecules to be used in designing novel and potent compounds with significant clinical value. For example, such compounds could be used in the inhibition of platelet aggregation and blockage of the tumor-induced platelet aggregation stage of metastasis. Disintegrins bind to the classical integrin proteins and block their actions, suppressing cancer cell growth, the adherence to blood vessel walls, and associated events which could reduce cancer cell metastasis [58,59]. Since GIP has been shown to suppress tumor growth and inhibit cell adhesion, it could be proposed that GIP might produce a disintegrin-like inhibition of cancer cell metastasis [57].

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Concluding Statements:

The suppressive growth mechanism of action of GIP appears to be at a level common to a variety of cell types since nine types of tumor cells were growth-inhibited [12,13]. Previous studies have also shown that the growth inhibitory effect of GIP can extend across species barriers and can be observed in lower animals such as amphibians, birds, reptiles, and mammals including primates [12,13]. These observations suggest a common inhibitory mechanism of action of GIP that is shared among many different types of human and animal cells [43]. In prior reports, the growth arrest mechanism of GIP has been ascribed to activities in the cell growth cycle and in the blockage of degradation of cell cycle inhibitors such as p27 Kip and p21 Cip (see below). The shared events of GIPs actions appear to initially begin at cell surface activities which can include cell adhesion, migration, aggregation, agglutination, cytoskeletal-mediated cell shape and form, and endocytosis [10].

Such conserved actions strongly indicate that GIP appears to be a cell surface membrane disruptive agent that can interface with or disable integrin-associated and platelet dependent physiological actions directed toward tumor growth, progression, and metastasis. It is evident from the present historical review, that an AFP-derived GIP is a major cell membrane disrupting agent at tumor cell surface events. Clearly, GIP is a capable suppressor of tumor cell proliferation demonstrated in both in vivo and in vitro rodent and human cancer models. In studies employing microtiter plate adhesion assays, it was shown that GIP inhibited tumor cell adhesion interactions against a vast array of ECM proteins, many of which serve as ECM interactors of basement membrane and blood clotting constituents [12,13,59,61-63].

GIP-coated coverslips were also employed to show that tumor cell attachment, migration, and spreading were negatively influenced by AFP-derived peptide actions. In assays using activated human platelet suspensions, GIP was shown capable of blocking all phases of the platelet aggregation reaction against a variety of agonist proteins. Overall, the inhibition by GIP in cell surface membrane activities such as tumor cell adhesion, migration, and platelet-binding could serve to significantly impair the ability of tumor cells to spread, migrate, and metastasize. But it was at the cell membrane that GIP demonstrated its most diverse functionality, by interfering with a variety of cell surface membrane events that could affect downstream signal transduction and receptor crosstalk. Furthermore, the growth arrest mechanism of action of GIP has been elucidated as an inhibition of the cell growth cycle as described above.

Declarations and Acknowledgement

Funding: None; no US federal grants were used in the preparation of this paper.

Conflicts of Interest

The author declares there are no known conflicts of interest in the preparation of this manuscript.

Acknowledgement

The author extends his thanks and gratitude to Ms. Sarah Andres for her commitment and time expenditure in the skilled typing and processing of the manuscript, references, and tables of this report.

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DOI: 10.19080/CTOIJ.2026.32.556340

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