Pharmaceutical Science and Technology
2026, Vol. 10, No. 2, pp. 42–55
https://doi.org/10.11648/j.pst.20261002.13

Research Article

InSilico Jargons~ Discussions & Amplification: Relationing with Colo Rectal Cancer

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Abstract

Background: Computational drug *alias* InSilico studies have become popular & dependable research planks. Basic & multi-disciplinary scientific-&-technical jargons are used aplenty. Clinicians of all levels & support resource persons are evincing interest to grasp. InSilico is a vague-bogus-Anglo-Latin term meaning 'experiments using computer platforms only' wherein 'platform' means 'software-&-hardware'. *Problem:* Computer involves all the sciences butted-&-bounded by humanities processed-&-packaged logically gets to be *jargon* full. Oncology also uses jargons and in InSilico either set of jargons converge. Jargons have remained unexplained and are mostly not understood; some at clinical level remaining incomprehensible completely. Regulators & all stake holders expect clinicians, practitioners, et al., to gradually grasp. Therefore, simple, lucid pedagogic & heuristic method is very necessary. There is no document that deals with InSilico jargons. Absence creates bottleneck between the (i) clinical query-&-the answer (ii) social-&-market needs and the effulgent researcher (iii) superfluous use of jargons sans a sense i.e., style ~ which makes lecture 'Great'. *Objective:* Use popular science model language to de-mystify all such jargons; and the ramification of use with ignorance and post grasp. Produce a 'Teaching Paper'. *Results:* Lipinski's Rule of 5 the corner stone of Computational drug discovery has been critically explained sequentially. Related jargons are amplified, elaborated & explained as independent sub-heading with background information. Thereafter, have been correlated with human gut geneTNIK (DNA) which is related to colo-rectal cancer (CRC). InSilico outcomes have been elaborated-correlated-and process of justification explanation has been attempted with. The APIs (active pharmaceutical ingredients) of the five most popular chemotherapy's drugs that are used in CRC (Capecitabine; Irinotecan; 5-FU; Taxen & Carboplatin) have been co-related; tabulated, discussed & explained. TNIK-&-APIs have been tabulated in inter-connected manner with sequence & logic in verse & tabulated. Mathematical interaction between CRC pathology's gene AND well known (non monoclonal) penta therapeutic APIs have been elucidated. Atoms; ions; energy; dimensions & Bio-physics at nano & pico scales has been attempted in verse; in Tables 'row-&-column wise' with multi-disciplinary uncenates which generates a illuminating 'column-row cross talk' for easy grasping by clinicians and patients (all stake holders). *Conclusion:* Scientific terms involve long syntaxes & polysyllables. Jargons reduce them to mono phones, thus are here to stay. Computational Studies - Pathogenic Genes - leading to API Discovery are high end complex multi-disciplinary sciences loaded with cutting edge terms with versatile moors in fundamental and emerging sciences. Thus attempted 1st conjoined teaching use of verse-&-tables vis-à-vis CRC & APIs with jargon demystified. 'Science-made-simple'.

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Received: 11 July 2026; **Accepted:** 30 July 2026; **Published:** 2 September 2026

Keywords

Biophysics OfInSilico, InSilico Jargons Amplification, Colo-Rectal Cancer & InSilico, TNIK, Wnt Gene

1. Introduction

Members of this multidisciplinary team have been stake holders in human health care in variable capacities & periods for three decades before present (within India). This includes QC; Toxicological studies; Geriatric; Refractile-cum-Complicated case attendance & nursing; Medical record keeping; Compound Screening; Medical meteorology; Public awareness; Functional food; Clinical service in the remote-rural and in large urban centers; Drugs discovery (also) involving 'computation\inSilico' studies, etc., with InSilico papers as outcome results [1]. This resulted in an ultra wide humane exposure. Everywhere the hands-&-minds at the clinical, support system and process levels were either jaded; wary or grappling and\or left nonplused with the jargons & technical terms that are used in 'InSilico Studies'. Many also dismissed us with a chuckle & jeer too often to 'mask' the reality. A few glossed over such gray-&-dark spots as 'communication problem' [2]. In disgust, to the www AI assisted search engine we raised the query "Clinicians Do not Understand InSilico Jargons?" and the 'Overview' scroll of the problem by the www AI sums succinctly [1][2][3].

The phone 'Computation' means numerical\mathematical modelling. And 'inSilico' means mathematical modelling using computers with special (pre)programmed software & AI, thus is in-vitro & theoretical. Pharmaceutical representatives are the link between clinicians & the manufacturers. They propagate the latest approved formulations; potencies; dosage; therapeutic effects; contradictions; regulator's guidelines, etc., in nut shell. Clinics are time compressed service units. Well packaged data is relied upon. Now-a-days, Pharmaceutical representatives have started citing Drug discovery & Drug validation concepts & data during their presentations which are non-clinical jargons. Drug discovery & therapy validation is an expensive slow flow work. Whereas, the same via computation is a fast track theoretical battle between the good of the human endeavor versus the gone wrong of the nature. Invention, discovery, designing and validation is done between the human engineered API's (active pharmaceutical ingredient) whereof atomic, subatomic, ions & para-magnetism etc., aspects are taken AND juxtaposed with the nature engineered (human) physiology's cell, organelles, genes, amino acid's, and\or the process intermediaries et al. In caption context all these are considered as causatives of Colo-Rectal Cancer (CRC). One of the current addendum is the use of AI [3]. Hence research findings get embellished with abundant use of jargons from the realm of high end basic & applied sciences, technology with new addendums aplenty at galloping speed. Thus, InSilico studies get to be delectable in detail, insightful with paradigm shifts and prised. Logically, clinicians have started evincing interest. On the other page the pharma company's representative also are not enabled so too the nursing and support resource persons. Almost all stake holders in the health care industry-&-services are wanting in such regards which results in wide gaps between the clinical query & the answer. There is a deep-&-urgent need to amplify the technical jargons as are involved in Computational studies of drugs-&-therapies. Amplification of the jargons is overdue. Clinicians need to know before they communicate via prescriptions.

1.1. Problem

There is dearth of light-&-literature about the (i) caption (ii) the palpable crisis of amplification with simplification of InSilico Jargons (iii) the term 'computation' is noted in all subbranches of the sciences while InSilico pertains to therapeutics (iv) to concurrently correlate with CRC (v) InSilico's role in Drug-discovery and 'confidence instilling' at clinical levels (vi) where is mathematics-&-physics in health care? (vii) where is engineering?

1.2. Outcome Result

For or the first time has been able to attempt & subtly part-answer the palpable & crying need of amplifying the inSilico jargons with simplification in a sequential manner along with

[1] "Yes, clinicians may not always fully grasp the specifics ofin silico jargon, as it often involves computational modeling and simulation techniques unfamiliar to many medical faculties. This gap in understanding can hinder the effective translation of in silico findings into clinical practice.

[2] Clinicians and basic researchers often operate with different sets of priorities and terminologies, creating a barrier to effective translation of research findings into clinical practice. Clinicians focus on patient care and treatment, while basic researchers explore the underlying mechanisms of disease & Therapeutics. This difference in focus leads to a gap in understanding and communication, where clinicians may find basic research jargon difficult to interpret and apply to their daily practice. Whence an situation is explained to a suffering it results in more synergistic combat towards victory.

[3] "Yes, there's a significant gap between the technical language used in~silico research and what clinicians typically understand. While in silico methods are becoming increasingly important in drug discovery, personalized medicine, and clinical trials, the jargon and tools are acting as barrier to wider adoption in clinical settings", says the AIOverview, 2025.

inter-connections between the various jargons and natural sciences concurrently connecting with CRC ~ the most predominant & galloping malignancy worldwide. Permits the stake holders of all levels of the health care industry's & even the non-initiated to peer into the myriads of aspects of the interesting domain of Drug Discovery & Regulations, clinical applications. The current best involvement of mathematics-physics-&-engineering (technology) with a scope towards upcoming possibilities stands highlighted (opportunities for the youth).

2. Lipinski's Rule

Computational study of drugs-&-therapeutics vis-à-vis diseased cell or its organelles known as 'docking-binding' exercise was developed byChristopher Lipinski inc. 1995-97 [4]. He set five parameters for inter corroborated validation work known as the "Lipinski's Rule of 5" [5]. If any molecule qualifies such penta parameters, it then is labeled as having 'likeness' for a possible drug moiety. Such penta-set test is among the most respected numerical route in current science. To be 'drug-like' *alias* 'likeness' a molecule should have (i) no more than five hydrogen bond donors (ii) no more than 10 hydrogen bond acceptors (iii) a molecular weight less than 500 Da (iv) a log P below 5 to ensure it is not too lipophilic and (v) should have rotatable bonds (Rot B). These penta are loaded amalgamation of bio-physics; chemistry; bio-chemistry; physics & mathematics. Should any molecule qualify such penta parameters then that molecules offer a 'likeness' to be effective as drug and is a good candidate for onward real time study & investments. A 'likeness' of less than 5 points in the direction of a failure (unlikely API). If the Lipinski's Rule of 5 is not done, then to arrive at such 'theoretical likeness' it would take researchers years and tens of time more expenses.

2.1. Cancer Amplified

Among the maladies cancer is a non-contagious, non-vector dependant natural process (non infectious); can be liquid or solid; afflicts all organs; ages; sex; geo locations, is borderless, limitless; requires expensive-painful treatment; with dominant commercial-diagnostic-&-service markets; yet mostly with grave prognosis. Cancer studies have been decorated with nine Nobles [6], one for 'computational protein design' [7] and non to CRC. Computation has extensively been applied in Cancer therapeutics [8, 9], also by this team [10] including CRC [11]. We noted that the associated jargons need enunciation & amplification in clinical cum popular science level.

Clinical levels love laconic lectures. What then is cancer from computation perspective? Cells contain a range of molecules which it rearranges at atomic level. This is a dynamic process and is essential for cell function and adaptation [12]. i.e., damaged cells can get corrected auto or if induced which is 90% of the natural order. Whence genes \ DNA (molecule) in cells become abnormal and live cells fully divides (mitosises) as robust muted cells it thence pathologically is declared as 'well differentiated' i.e., malignant. Damaged genes may or may-not generate muted cells. In investigation reports the description 'well differentiation' means a mass (onko {Greek phone}) comprised of variedly laid cells alias cancer. Cancer genesis has conclusively been related to 'gene gone wrong' [13]. The more causative being systemic incessant mitosis of'robust abnormal genes' i.e., genes with permanently altered atomic arraignments in the DNA [14]. Genes\molecules\DNA being comprised of atoms the atomic composition, radius of the spins can alter due to insult & various stimuli. Physiological processes mounts defense against such phenomena i.e., cytokine storms happens which normally inflicts corrections & repair in continuum and per chance may fail resulting in tumor\cancer. Cytokine storms are of various order during status cancer and when medicines are introduced can antagonize or adjunct resulting in swing in status i.e., 'response pathology'. Drug engineers factor all this in.

Whence, 'gone wrong gene' overcomes physiological defense & correction onslaught even when aided by pristine life style and abetted by nice medicines a cellular mass (solid\lqd) comprised of 'gone wrong cells' can come into situ alias onko {Greek phone}). This is 'oncogenesis'. Tumor alludes to settled onko. It is non motile. 'Meta' is the Greek phone for the whole physiology (entire frame). When onko post genesis gets transported by physiological processes from the 'primary' genetic location to any other wherein it re-settles down elsewhere as onko (active-effective) it is termed as 'metastasis' or 'secondary'. Solid cancer constituents can get vectored via blood\lymph and can onko elsewhere only as solid metastasis. Solid-to-blood cancer happens not. Solid-to-lymph cancer is part of the process. Blood to lymph cancer is normal. Lymph to blood cancer happens not. Between the 'primary and the 'secondary' there can only be two vectors, namely blood and lymph. Such vectors are also comprised of numerous cells so too be the types of liquid cancer (as alike solid). All cells of the human physiological processes offer opportunities for onko & therapeutics. The more be the 'differentiation' the higher is the stage of the cancer (graded as I-to-IV^{+}). The greater shall thence be the variation required in therapeutics. All this holds good for CRC. From computation assisted drug discovery & applicability (likeness) perspectives the atomic interactivity between the API and the TNIK (the gone wrong gene of CRC) be the consideration. InSilico is the in-vitro theoretical gaming exercise to hold aloft such interaction as numerical values. Genes work at atomic level. InSilico computation is also done at atomic level. An understanding about such interaction is most sought by the stake holders. Laconic lectures gain never before lucidity whence jargons are grasped.

2.2. Jargon's Pedigree

Health care science is heritage. Why, wherefrom & how

new (outlandish) jargons in health care science? In therapeutics the involved biochems are known as kinase; genes, proteins, etc., being expressed copiously by malignant & healthy cells alike, unequally though. Computational studies discounts kinases, et al., effluxed by healthy cells and accounts only the 'gone wrong cells & organelle'. CT-APIs are human engineered moieties of 'n' number of types-&-makes in varied configuration that antagonize the kinases which are produced by 'gone wrong cells & organelle'. Kinases are ion potentiated; and whereas APIs may be ionic or non depending upon the engineered objective\s. All cells of the human physiology oscillate-&-vibrate however malignant cells do more thus the organelles of the malignant cells have a greater agitation (natural frequency ~ ω_n) & energy quotient than the malignant, becausing a frequency gradient. APIs do not vibrate until they dock onto any cell or to any organelle\kinase. Now, docking followed by binding between the malignant and the APIs happens only at atom level; the sub-atomic level being the ions associated with such atoms. Ions love opposite partners (charge). Only whence in close proximity (500-100 pico-meters; Table 2 represented as Å 'angstrom') they prefer to embrace; copulate; cohabitate and remain locked & flock together. Such copulation & API\drug delivery is (near) enrichment phenomena that results in exponential conversion of potential energy into kinetic and in 'flash' attainment of a very large quanta of energy and work done ability (vis-à-vis instant environment i.e., size-mass-vol, etc. Kinetic energy means motion propensity. All genes, kinetic processes (kinases) are signal dependent and in-vivo signals are ions [15] with nano-ampere electricity. Furthermore, each can vary with shifts (have assumptive range) - natural phenomena. Moreover the whole blood, it's cell components are not affected by gravity. From therapeutics all these are relied upon to draw the API into the cancerous cell. InSilico focuses on such natural phenomena and tries computer-software assisted gaming known as computational study of (proposed) new moieties & validation of the existing. All such Such Drug-pathology interaction exercise is done *in-vitro* on desk top computers. Logically brings new jargons into usage. The vital harvests have been nomenclatured as "Binding Energy" (kcal/Mol in minus numbers);"Ligand Efficiency" (the ion gradient between the API & the CRC\malignant cell in minus numbers);"Inhibition Constant"(in micro meters); "No. of H Bonds" (drug delivery bridges alias the projected {almost sure} number of to-&-fro working vestibules for drug-&-cancer cell interaction);"H-Bond Forming Residues" (are amino acids on[4] the cancer cell\organelles); "Average Distance of H-Bonds" (being stated @ Å when 1 Å= 100 pico meters and be the optimum separation at about which embrace-copulation-&-exchange occur).

For computation all this necessitates modified mathematics (geometry included). Lipinski did that. 30yrs old heritage with full axial connections. Each of these aspects are apportioned nomenclatures (jargons) as they be the distillate of a plethora of known propositions & processes thereof; all surreal and close to happenings within the physiology. In this communication such jargons make the banner lines to form Table 2. The token pathology member is CRC represented by it's gone wrong gene TNIK. Computational numerical vetting unlocks the gates of suggestion for new drug or about the validity of a therapy for which docking & binding exercise is due. Even a rudimentary grasp enables the clinician to attempt any neo-adjuvant concept; clinical gaming; drug discovery & standardisation of operation procedure\s (SOP).

3. The Problem: CRC – TNIK Nexus

3.1. CRC-TNIK

Worldwide CRC is the major among the malignancy types and is galloping [16]. TNIK TRAF2 and NCK Interacting Protein kinase (T= tnik; N=nck & IK=interacting protein kinase which has been summed up as TNIK) is a 'robust abnormal gene' and thus far is held as the causative gone wrong gene in CRC. Wingless-related integration site (Wnt) signaling is an inter-&-intra-cellular pathway. It is evolutionary i.e., natural. Both, Wnt and TNIK are asyclically expressed from brain-to-planters & pervades & permeates the whole physiology, all processes, all organs, embryo genesis, neoplasia & apoptosis [4]. TNIK is innately dependent on Wnt pathway for (any) neoplasia [17]; specially CRC. And, process\phenomena Wnt is in deep down-regulated state in status CRCdue to functional loss of adenomatous polyposis coli [18], whereas TNIK gene is thence in a state of copious expression [19] i.e., 'Wnt is in down-regulated state of expression and TNIK in up-regulated state i.e., inverse condition' = ideal for tumors\malignancy\threshold fjord (as base is involved in phenomena Wnt which occludes\attenuates signals?).

Found life style is the causative for mid-gut scarring and leads to end gut malignancy. Once cancer is in situ therapeutically inducing an up-regulation of Wnt expression does not lead to anti-cancer efficacy –grave prognosis remains large. Antagonising TNIK with therapies does cause (i) direct negation of circulating\settled oncogens (ii) up-regulate Wnt to normal levels (iii) open windows for economic multi-drug usages i.e., more choice for the clinicians (iv) easy to make; environmentally stable; cold chain not requiring compounds (v) sub-clinical dosing i.e., non bolus\non loading (vi) better tolerance & compliance (vii) patient retention (viii) may be even prophylactic by-&-by. TNIK is expressed the greatest in the brain and 3rd highest in the intestine. Currently world wide TNIK is the 'target-gene' for drug discovery[1]. Moreover, sedentary, food, lifestyle with/without professional tension and brainy function is a good recipe for imbalance between Wnt-&-TNIKin other words more-&-more CRC in our societies in

[4] Wnt proteins expression (are vary-&-many) & its antagonists\suppression regulate almost all cellular processes including cell fate, organogenesis motility, polarity, primary axis formation and stem cell renewal.

coming decades. The main causative in CRC is the TNIK. It is a gene (DNA block\bundle); is a compound member and a compounder also !It is abundant in human physiology as a great voluntary contractor of unlimited good construction and controlled destruction ~ canonical. InSilico offers a economic-safe-swift route of study.

3.2. Wnt

Wnt = wingless (literary-adverb). Inspiration is drawn from fruit flies that rocket onto fruits and bore in for safe-housing & progeny (result? = rapid fruit rot). t = integration i.e., integrated action i.e., the fruit's aril-&-nutrients also co-participates. Now, in pre status CRC the TNIK gene is a self balancing\regulating block DNA. It develops a missile\projectile property alike wingless (as in Mig-27 swing wing bomber; or glide bomb). This gene can bind to the RBD of each cell of the colon-rectum segment of the gut via RAF No. 1 (*alpha*) for good cell health AND onto RAF No. 2 (*beta*) for inducing systemic cell death selectively as per physiological need (RAF = Rapidly Accelerated Fibrosarcoma). Such select need-based binding epitomises interactive signaling and is known as the Wnt ~ dominant in all animal\human physiology as an ever present galloping process. It is natural & cardinal = phenomena. Such phenomena (*kinase*) manifests one at a time (both not together). Kinase\natural activity with RAF *alpha* and RAF *beta* are also known as Wnt/*alpha* and Wnt/*beta*, respectively. Former is associated with the Zwitterionamino acid Serine & Threonine while the later is associated with Catenin a non-ion i.e., base. Between the two, the TNIK *gene* and catenin kinases involves 'high energy' and 'high speed' (comparative very large). Process\kinase Wnt *alpha* is tumor-necrotic (apoptosis inducer), is gut health harbringing, and embryo-genetic. It prevails all the while. Process Wnt *beta* manifests once in a while and if such kinase continues at any site it becomes onco-genetic[5] (strange neo mass). Why? Catenin = is a component of the cytoplasm of any cell and is an effulgent chemical (as it is a broth type & base in charge). It is a target fluid bed for ionic members such as any gene\DNA (particularly TNIK); toxins or carcinogens however small as these are highly ionic. Catenin expression from within any cell line onto its own ligand's RBDs is synaptic *interalia*gut brain\vagus nerve involvement is the rule (own latest). Also, excess expression of catenin from within any cell line onto its own ligand's RBDs silences RAF-*alpha* (1) and efficiently upregulates RAF-*beta* (2) activity on such RBD (rule of exception e.g., trauma; chemical insult; etc.). Post sustained synergic activity between RAF-2 & Catenin (on the RBD) rapid penetration of cell by insulting\deforming\ DNA moieties proceeds assilent-painless intra-cellular boring resulting in pleo morphing becausing 'swift silent stage malignancy' which all on pathological slides are seen as 'well differentiated' and via radio\resonant images as 'in-situ'. Such 'boring' phenomena is'jump start' of cancer in general and CRC in particular which clinically & even diagnostically is detected only in advanced stages as a significant adenoma &\or as invasive carcinoma. In francophone, researchers have termed such phenomena\kinase as '*portmanteau'* (porter of disaster). Hence, there is an urgent need to also elaborate CRC associated collateral jargons viz., Wnt in these presents. Therefore, clinical management may include 'gut health' so that catenin manifests not on the cell ligand's RBD deleteriously (particularly during Chemo-therapy cycles). Clinicians shall have to factor-in Functional Foods & combat better. OUR WORK: status Wnt (RAF-1 activity lessening) in turn may have a nexus with vagus nerves & excess availability of oxygen (read with *Functional Food;* at .6).

3.3. Objectives

In this study-cum-teaching paper the primary 1st & 2nd objectives are to amplify and explain InSilico related Jargons and conduct an InSilico assay with current most five popular chemos as the antagonist members, respectively. The secondary objective is to place the assay data in tabulated form and make comparative evaluation of the digital performance of the 5 APIs. AND, additionally try to throw some light on as to how the tabulated data can be helpful to correlate the jargons with therapeutics. THUS profit at pharma & clinical levels.

3.4. Five Antagonists

Capecitabine; Irinotecan; 5-FU; Taxen & Carboplatin.

Table 1. *Description ofthe 5 Popular Drugs.*

CulmNo.	**1**	**2**	**3**	**4**	**5**
RowName	**Chemicalname**	**Molecular-Formula**	**Molar Mass**	**PMID (PubMed Central Identifier)**	**SMILE ID (Simplified Molecular Input Line Entry System)**
A	Capecitabine	$C_{15}H_{22}FN_3O_6$	359	60953	CCCCCOC(=O)NC1=NC(=O)N(C=C1F)C2C(C(C(O2)C)O)O

[5]Adenomatous polyposis coliloss can be grappled significantly with 'functional food'&'complementaryregenerativeinputs'.

CulmNo.	1	2	3	4	5
RowName	Chemicalname	Molecular-Formula	Molar Mass	PMID (PubMed Central Identifier)	SMILE ID (Simplified Molecular Input Line Entry System)
B	Irinotecan	$C_{33}H_{38}N_4O_6$	587	60838	CCC1=C2CN3C(=CC4=C(C3=O)COC(=O)C4(CC)O)C2=NC5=C1C=C(C=C5)OC(=O)N6CCC(CC6)N7CCCCC7
C	5-FU	$C_4H_3FN_2O_2$	130	3385	C1=C(C(=O)NC(=O)N1)F
D	Taxen (Paclitaxel)	$C_{47}H_{51}NO_{14}$	854	36314	CC1=C2C(C(=O)C3(C(CC4C(C3C(C(C2(C)C)(CC1OC(=O)C(C(C5=CC=CC=C5)NC(=O)C6=CC=CC=C6)O)O)OC(=O)C7=CC=CC=C7)(CO4)OC(=O)C)O)C)OC(=O)C
E	Carboplatin	$C_6H_{12}N_2O_4Pt$	371	426756	C1CC(C1)(C(=O)O)C(=O)O.[NH2-].[NH2-].[Pt+2]

This Table has been partly produced in our own work Ref – 11 ~ as run-up to this communication.

3.5. Docking: Computational Assay Results

Table 2. Docking the 5 Drugs against TNIK protein of CRC using Autodock 4.2 tool.

ClmSl. No.	1	2	3	4	5	6	7
Row Sl. No.	API	Binding Energy (kcal/Mol)	Ligand Efficiency	Inhibition Constant (µm) Ki	No. of H Bonds	H-Bond Forming Residues/RBD	Average Distance of H-Bonds (Å)
1.	Capecitabine	-5.56	-0.22	83.58	4	TYR36, SER112, THR35	2.5714525
2.	Irinotecan	-10.5	-0.24	20.04	1	CYS108	2.78146
3.	5-FU	-4.5	-0.5	498.71	5	LEU50, TYR86, PHE107	2.55598
4.	Paclitaxel	-4.25	-0.07	766.88	1	LYS310	2.8698
5.	Carboplatin	-4.21	-0.42	822.38	2	LYS41, LYS310	2.62224

Note: TYR & LYS are the most common amino acid binding residues. 5FU alone has PHE (maverick member). RBD receptor binding domains. Table produced in our own work Ref – 11 ~ as run-up to this communication.

4. Jargons

4.1. Ligand

Cancer cell (CRC herein after) surface alike the non cancerous are full with ‘ligands’ - a (near) permanent cantilever i.e., port. Ligands are vestibules of size ranging 200-350 cubic nanometer. It is a tool to trap food\APIs by ionizing as they float around its external end which results in the conversion of the API’s potential energy into kinetic with fold jump in energy [1]. Ionisation results in the docking of the API (initial bridge formation). While (non-deflective\ bi-polar) energisation results in the formation of a ‘bond’ post which the API gets translocated into CRC cells (via TNIK domain). The trunk of such bonds be the ligand. It is a bridge with a lumen (partly jelly filled vestibule i.e., ion gel) with a metallic moor - Fe atom the most. TNIK gene and API’s proteins are comprised of amino acids which contain ions which have bi-polar energy as electrical charge. This energy is used (by the physiology 24x7) to bind. Drug designing engineers alter the (a) ion (b) potential energy content of an API to attain targeted binding (c) CRC cell’s surface & TNIK also have an ever present ion, potential & kinetic energy which is much greater than a+b. Ligand is flexible, complex, commanding & hard ware tool that can keep doing docking-binding delivery-jobs in continuum for a variety of APIs. Ligands are nature designed for polygamy. Now, ligands contain ion-gels, are non-newtonian fluids, act as excellent para-magnets (due to high energy of the host cell), conductors, permits electrons (sub-atomic particle) to perform as Bosons (pack together); do not suffer shear nor deflection;

is a phenomena - primarily due to absence of gravity (gravity effect is virtually nil in capillaries & cells). Nature's preferred make. All this can be numerically visualized in the InSilico.

4.2. Binding Energy

Energy is a dimension which on ionisation acts as the vector. Hence a+b+c = d = Gross energy that manifests at moment binding post docking.a + b component is human engineered. 'c' is nature engineered. Hence is a large number on the negative scale (T-2, Clm-2). API is the antigen & TNIK is the anti-body. Binding between API & TNIK can only happen whence the a + b component is less than that of the 'c' i.e., a energy gradient from anti-body towards the anti-gen (from CRC cell's TNIKtowards API). *Inter-alia* 'a+b' should not be deflecting 'c'. It is a situation\phenomena. The amount [6]of energy needed for binding is so miniscule that it is always in the range of negative Joule. The optimum range of such gradient is between (-)8.0 to (-)11.71 kcal/mol. 'a-to-d'are negative Joule masses; a sub-tool or software (API', ligand, TNIK being the hard-wares). Binding energy is a 'dimension' cum 'vector member' for the API to fjord via the ligand onto the TNIK'sRBD and then pass into the CRC cell (inoculation). At inoculation instant the ligand's RBD is also ionic and offers an electro-chemical gradient – which is a component of the 'binding energy' dimension. Such component should offer 'affinity' and not be antithetic.

"Binding Affinity": The components of 'binding energy' are (e) mass of the API (f) length of the Ligand (g) time\gradient (for drug inoculation). TNIK's ligand's RBD is (intently) ionic and at docking instant offers a counter 'ion gradient' (electro-chemical) for ionizing the API and thus the RBD rapidly lose ions and ionically alters own status towards 'less or neutral'. No. (e) & (f) are the vector component (of the energy dimension) and have a one way phenomena association (g) is a two way phenomena and is the time unit of the 'binding energy's' dimension. No (g) i.e., time unit has to be so that the RBD offers affinity to the API post docking for an effective binding (for drug delivery). Thus (e) & (f) offer energy and (g) creates affinity (relative).

Whence 'Binding Energy' is a large number (negative scale) thence 'binding affinity' is good. Computationally it means, at that moment there are no other competing or impeding conditions (no electro-chemical repulsion from the RBD towards the API post initial docking). It is a shadow value (not shown in Table). 'Affinity' does not mean 'efficiency' nor 'sure binding' it only means 'likeness' of good docking-translating to good bonding-translating to effective API delivery (even then it means not 'kill\cure'). Theoretically, a deep negativebinding energypoints towards a 'large magnitude of the API-TNIK interaction', which in turn spells good 'ligand efficiency' (add-on likeness) for the assayed API~correlate with 'Ki'.

4.3. Ligand Efficiency

Above 3 parameters may be there yet the docking-binding can wilt-falter-fail = inefficient. Whence the trio parameters are considered conjointly 'efficiency' comes into play. Hence efficiency has to be calculated. Now, the ion gradient between the API & TNIK can be steep yet the API & the TNIK may indicate same ion charge *and\or* has a quasi-crystalline for-m*and\or* the RBD's platform may be hydrophilic *and\or* the API may not be at all Lipophilic *and\or* the API has a obstinate base and\or the ligand's vestibule is frail-or-fissure full; etc., i.e., some at site "competition" (deflection included). All these points in the direction of 'competition' for the RBD. Ligands love monopoly, competition is not tolerated.

We have earlier used the term 'polygamy\ *polygyny'* which means the ligand's RBD selectively permits docking with 'n' number of APIs sans any interference from non APIs. 'Competition' means 'polyandry' (*Bahupatitva* as in Sanskrit?) i.e., presence of other non APIs competing as eligible candidates for docking and or interdicting API docking onto the RBD (signature of pathological condition). Absence of competition (other eligible candidates) results in status 'affinity' between the RBD and the API which therapeutically translates as 'efficiency'. A case of marriage rings.

In drug deliver, clinically, developmental biology & in recuperation atinfirmary 'competition' is the recipe for failure (embryogenesis included). Absence of competition (from non APIs) for the RBD is 'ligand efficiency'. The greater be the 'ligand efficiency' number the better gets to be the API's 'therapeutic index'. Energy & Affinity are large numbers and as they are mathematically-theoretically antagonised by competition conditions transpire as a factor. Therefore, the larger be the negative number the better is the Efficiency (T-2, Clm-3).

'Therapeutic Index': Every drug is administered on 'dose' basis. By increasing the quantity and\or the concentration of each dose it can be made more toxic to the native physiology in relation to weight; mass; age & age. It is written as a ratio between toxic dose divided by effective dose (TI = TD50 / ED50). A number greater than 10 means the drug is very safe, while a number below 5 is risky.

4.4. Inhibition Constant Ki

T-2, Clm-4. Herein 'inhibition' means any (inbuilt) potency of the API to thwart its own RBD activity whence computationally assayed. Therefore, the smaller the Ki number the greater is the 'likeness' possibility. As the blood\physiology gets loaded with API (during therapy\CT cycles) inhibition induced by that very APIs towards reception-docking-&-binding (RBD activity) has to be low-&-sustained which logically is a 'constant (mathematical series)'. The small be the number better be the binding stability (Table 3, Clm. 7). In caption

[6]Any flexible vestibule that complexes one atom at a time is a 'ligand'.Its process is ionization that alters the API's (atom's) entropy state to enthalpy. Whence any ligand is in a state of peak efficient function $E=mc^2$ mechanics comes into play. This generates energy (which is necessary).

context it is a stability indicator and relates directly to clarity of the vector field between the API-&-TNIK. The deep is the negative charge the better be the (h) ease of availability ofion-energy dimension (i) vector field – ligand lumen (j) likeness of the invite signal from the TNIK to the API. All cells for self sustenance are naturally ordained to 'receive', malignant cells the more. Ki is the signature of the vector field's clarity less (competition-&-interference). APIs for any one of these reasons shall indicate a large Ki number and indicate less likeness in-spite of large negative binding energy & ligand efficiency. Portend as toxic; pro inflammatory. Ultra large API compounds; have more nitrous oxide (NO) atoms.

'Disassociation Constant' Dk. Not shown in Table. Dk means that due astute engineering how much a API assist its own docking and thereafter retain 'binding' status post 'docking' onto the ligand's RBD. In other words, greater the Dk value the better and less contribution to 'Ki'. If any API is showing low Ki and high Dk then the 'likeness' is best. Even then there are other frailty~fail inducing factors viz., isotopes; heavy metal atoms; too many heavy atoms; isoelectric point (pI); pH, etc., as these also influence the negativity of the charge (adverse effect on energy dimension). So too APIs self develop foibles in banking veins as compared to turbulent-laminar flow veins. Dk is dependent on 'atomic composition' (drug engineering). Low Dk indicates less likeness (i.e., fail post even post initial docking & binding). Clinician can never get to know. Nightmare!

Taking Ki or Dk (any one) into consideration suffices in computational studies. Drug design engineers & validation authorities take any one into account. Nevertheless, either are not opposite numbers; nor are each-other's shadow; neither do they vet each other; yet are relevant for the docking-binding studies for very different reasons. For very large compounds (Bevacizumab?) get a thumbs down Dk value and a thumbs up for Ki ! = in varying physiological challenge can go 'hickory-dickory' = scope for propaganda to rule. For small compounds (T-1) Ki-&-Dk gives a 'thumbs-up' or a 'thumbs-down' uniformly= least propaganda needed by Team sales.

4.5. Heavy Atom

'H' i.e., hydrogenis a light atom. All other atoms are the 'heavy' atoms.

4.5.1. No. of H-Bonds

H atoms are the lightest & fleet. CRC\malignant cells have abnormal levels of H atoms as compared to adjacent healthy with all cell orientation in 'disarray'. Small molecule APIs have few H atoms and are well ordained. H atoms do not approach each other equally from the API & the Ligand; approach\affinity has to be on opposite charge basis. This is known as non-covalent bond. Copulation happens due to energy gradient & ion signalling (to-&-fro) i.e., good 'ligand efficiency' and the API makes a donation of its well arrayed H atoms onto the TNIK afflicted cell'sRBD (that to) at preferred landing sites (being small molecule size the RBD offers alternate docking sites). Comparatively, the TNIK\malignant cell being in higher state of agitation has more H atoms with larger atomic radius i.e., 'disarray' = H bonding. API's H atoms thence has to be compact. Only then the API can receive less, donate more i.e., non covalent bonding. Such bonds are one way actions; unstable & of short life. Hence, on one hand facilitates and on the other there is a necessity for more number of bonds for efficient transfer of the mass (API) dimension (energy) along the vector (ligand) @ one way gradient i.e., 'affinity' (time) = fleet. The RBD being of concavo-convex architecture is 'area-limited' to incident activity (docking) in dynamic fluid bed (hemodynamics). The optimum has therefore been worked out to as a maximum of 5 H bonds. N (nitrogen =heavy & inert) and too many H bonds competing for the same RBD site adversely affects 'ligand efficiency'. Such aspects has been considered as infirmities in InSilico – as it mathematically results in inefficient delivery of API.

4.5.2. H-Bond Forming Residues

Ligands have 2 terminals one is moored into the CRC's cell wall and the other has the concave-convex RBD being exposed to latch APIs. The exposed platform is convex in architecture to maximise surface area for dock-bond-deliver-interaction. The physiological process reduces the APIs to atomic size (famto meter scale) while the RBD is of nano scale i.e., few thousand times larger (whole residues can reside on such vast platform). It is a preferred design; and contains the amino acids of the TNIK gene that all be the 'bond forming residues'. The H atom from the API gets subsumed into these amino acids and sink into the pathogenic cell on fording the ligand on basis of opposite charge para magnetism. The amino acid are comparatively large than the H atom of the API and also offer numerous H receptors thus one residue can form more than one bond – is a case of polygamy. Thence, 'affinity' is must i.e., absence of competition i.e., zero polyandry. *Interalia* polyandry at RBD = ligand inefficiency.

5. Non Covalent Bond

Therapeutic H Bonds happen on the RBD between the API and the amino acid residue with +ve and (-)ve charges at opposite ends. Electrons i.e., (-)ve charge ions from the highly potentiated & pulsating CRC move up along its own ligand onto its own RBD to form immensely activated amino acid residues. The terminal ends of the APIs are normally charge depleted and dock with the high energy amino-residues. It results in an unstable electron configuration and ions (charge) flow back-&-forth along the vector path (ligand') to propel the therapeutic compounds at atomic level. There is no sharing of electrons. Hence, non-covalent. Work done, the bond lapses; non permanent. One of the fine contrast between covalent & non covalent bond is that in the later type at pico-&-nano scale extreme high energy based work done is possible in wet and or semi conductor conditions sans any metallic conductor.

5.1. Average Distance of H-Bonds

The mean separation between two H Bonds ranges between 2.3 and 2.4Å (angstrom). One Å =100 picometers (1mt ÷ 10000000000 = 1 Å or 10 nanometer) thus 2.3-2.4Å works out to 230-240 pico-meters or 0.2 nono meters. Less than this [7]= compaction; more than this = disarray. This is the average inter bond distance on the CRC's Ligand's RBD. Less than this = competition\polyandry = API ligand bonding infirmities. More than five bonds means polygamy phenomena = [8]wavering therapeutic returns at identical clinical conditions. Average distance of H bonds means radius of the H atoms. If the H atoms be in a state of disarray i.e., have larger atomic radius say >400picometers it means less competition\less polyandry also = better 'affinity' = favourable for establishment of more H bonds (also polygamy possible). On the RBD more than one bond can happen viz., small molecule APIs (e.g., Fu which has surface area of 5800 square picometers) tend to form more H bonds and get delivered across the ligand bridge relatively more swiftly. In computational studies if the number of the H bonds be more it then means the corresponding API has not elicited any compaction rather is pointing in the direction of larger atomic radius. The average cross section of the penta API's protein molecules (T-1) is 10000 picometer. CRC cell's mean surface area = 16,000,000 square picometers means a CRC cell has a lot of space. However the ligand's height of 2000 picometer and internal volume of 6000 square picometer is the drug-per-dose controlling factor. Nevertheless, ligands can flash expand significantly as it is a 'High Energy' vector cum ultra flexible vestibule ~ polarized & semi-conducting (else? power failure\bridge blow).

5.2. High Energy Bonds

means the same therapeutic non covalent H bonds as amplified herein above. CRC or any malignant cells are intently (-)ve in charge means the API's any one or more terminal should be a loaded (+) ve. Also of low charge! Else, docking will happen yet bonding shall be inefficient. Why? because CRC cell's are among the highest energy potent. Ligands being non-covalent bonds are weak yet handle 'high energy'. How & why? The APIs as in T-1 have an approximate size of 150-550-850-300 Daltons, respectively; weight range of 2.5^{-16} to 1.5^{-15} micro grams; spherical diameter range = 0.7 to 1.3nM and are charged compounds [7]. Forexample, the molar mass of 350 Dalton (T-1) =522000000Joules. It is a small molecule. On attachment even such API has to remain well conserved while traversing the ligand's length dimension of 2000 picometer and the volume of 6000 square picometers in 20nS. The whole ligand gets-&-remains full-loaded & weighted with (high) energized mass resulting in exploding condition\s. Thus, 'high energy @ high speed = high energy bonds'. Moreover, a single CRC cell in-vivo has a diameter of 125000,000 picometer; 1000-000 picogram as its weight and a mass density of 100 picogram per square microgram [8]. On the other side (post ligand vector phase) for inoculation past the OM of the CRC cell high speed-&-thrust are essential. Hence, API vectoring happens at an ultra speed of 20nS (natural design). Delay is fraught with difficulties. Once the ligand bridge is passed in an eventless manner the cytoplasm offers huge space to the API (settle down). Furthermore, 350 Dalton appears as the cut off for 'stress free'; 'damage free', delivery\work done by the ligand. Toxic API do not damage ligand (per say) – affects OM & cytoplasm\organelles. Whereas, APIs with large energy quotient, size, mass do. Vector speed is of importance from cell wall fjording & over coming cytoplasm's hydro-static pressure, etc. High energy bond' is a Pandora's box (full of forward engineering & inspirational opportunities).

6. Functional Foods

The following Functional Foods are under active consideration by this team since 1990.

6.1. Target Vagus Nerveand Objective A

Prevention and thwart in threshold cases or in relapse chance cases:(i) *Scaphium affine* (tropo-equatorial fruit) if consumed as a whole post soaking for 6-8hrs in potable water of 30-35deg centigrade and\or its Bio-active compounds *Sterculinine*-I & II; alkaloid with formula $C_{18}H_{20}N_2O_6$ andMolWt of 360 Daltons (ii) potash alum*Potassium Sulfate**Aluminum Sulfate* K_2SO_4 & $Al_2(SO_4)$, respectively. Aluminum hydroxide yields the reverse. POTENCY: ~1-5gms dissolved in 1 Lt of deionised, de-mineralised, distilled, sterile water. Dose: 100 ml\day, any time post prandial; with wash down intermissions.

6.2. Target Neoplasticsand Objective B

Neo masses if any that may have formed in the elementary canal or anywhere due Wnt\TNIK et al., activity). Objective? regression. Result = Anti Tissue activity on the neoplasia. Wild/pea eggplant i.e., all sister species of *Solanum*viz., *virginianum* \ *Sisymbriifolium* & bio-similars & bio-compounds (particularly the one that grows on river beds - mini & midi thorny berryvig. Khordha Kanta Baigana). PREPARATION:

[7] most of the octa fjords the Blood Brain Barrier (BBB). A compound post fjord can induce the physiology to respond in a deviate manner. Hence continuous close feedback based noting can be done by FPs.

[8] The APIs of our octa have an potential energy of the range 1/5000-to-1/10000thfraction of 1 Joule; the kinetic form being 500-to1000 micro amperes @ same volts (= 1 micro ampere for every 0.000000005 nano-cubic meter of the ligand = hence explosive). Yet in circulation stage such large potential energy as are in the APIs do nil-work.They lung forward only post ligand attachment. Ligand is a very special lumen that converts the API's potential energy to work done ability @ high voltage in a flash and reconverts the API to its parent form with no alteration in spin (full conservation). Table 3 helps in indicating all this to the informed mind & the critical eye.

burnt; roasted; fried with clarified butter one full dish on alternate days and or smoke inhalation post bellyful food\fluid. Superb with Chemos. Prophylaxis? Yes, for all above. How to locally hold or at site concentrate a gut scavenging\target drug? Soaked Basil seeds.

6.3. Danger

(1) Colocesia\ any sister species & bio-similar\chiral compounds inclusive (2) Iodine including iodised salts. NOTE: we mention these so that all stake holders may feel free to exploit and build upon our three-decade long use based findings. Ask~join author-1. Read with No. 3.2.

7. Discussion (*Jargon*)

In cancer (general target) & CRC (specific target) from among the above parameters 'high affinity'; 'binding energy'; large 'inhibition constant'; hydrophobicity; Iso-electric; and 3D arraignment of the atoms = Ideal. Cumulatively these also make & sustains the 'high energy bonds' which is essential for early, efficient and long duration binding culminating with efficient API delivery. The relationship between the TNIK and any API is a poly-parameter function and is also known as CRC's ligand. It is not merely a bridge, it is a versatile dynamic member. It functions at high energy & ultra speed. The more ordained these parameters be the better for non-covalent ligand to initially form a bridge thereafter act as a vestibule for high speed transaction at high energy a donor-receptor job window of 20nS along a length 250-350nM with the API well conserved.

In therapeutics API attachment & delivery is underlined by (i) multi-member; poly-angular synergistic work involving (ii) mechanical forcing (iii) bio-physics & bio-chemistry (iv) ion-exchange & above all Para-Magnetism.

7.1. Internal Observations

We now revisit Tables 1 and 2 and attempt yet another tabulated presentation (Table 3) with discussion. This Table talks the interaction outcome results in mathematical language and the relevance of the 5 drug compounds vis-à-vis CRC and further indicates as to how inSilico study helps in throwing some light. It is a sort of steganography approach to appreciate the embedded data and to make eloquent the silent.

Table 3. *Internal Transpirations of Tables 1 & 2.*

	1	2	3	4	5	6	7	8	9	10
A	*Capecitabine*	$C_{15}H_{22}FN_3O_6$	24-&-22	1:0.9166	-5.56	-0.22	83.58	46	4	11.5:1
B	*Irinotecan*	$C_{33}H_{38}N_4O_6$	43-&-38	1:0.8837	-10.5	-0.24	20.04	81	1	81:1
C	*5-Fu*	$C_4H_3FN_2O_2$	8-&-3	1:0.375	-4.5	-0.5	498.71	11	5	2.2:1
D	*Taxen*	$C_{47}H_{51}NO_{14}$	61-&-51	1:1.2	-4.25	-0.07	766.88	112	1	112:1
E	*Carboplatin*	$C_6H_{12}N_2O_4Pt$	12-&-12	1:1	-4.21	-0.42	822.38	24	2	12:1

Column: 1 – API; 2- Formula & MW; 3-Heavy atoms & H atoms; 4 – Ratio between Heavy & Light atoms (H); 5 – Binding Free energy or Docking score; 6 – Ligand efficiency; 7 – Inhibition constant; 8 – Total No of atoms; 9 – No. of H bonds; 10 – Ratio between 8 & 9. Row A-to-E give the meta data of the APIs that have been taken to conduct the computational study AND the select\relevant transpirations.

7.2. Row Wise

The theoretical docking outcome (values) for any given API can be observed & studies in a scroll out manner.

Row – A: Is an API for oral & IV route of applications. Only in geriatric and in underweight IV is considered. Is a beauty in stage 1 \ or silent stage applications. The combination of large number of H with FN atoms makes it toxic; FN imparts good ligand efficiency on one hand & on the other lowers its inhibition constant; can impart instability.

Row – B: This API (alike the member in Row D & E) clinically shows good-to-best out-come results on 1st onslaught. Its 'inhibition constant' being low surmises the causes of its inconsistent results. Theoretically its inSilico numbers are not resonant save-&-except 'ligand efficiency'. N is the cause of its large inhibition constant.

Row – C: This API indicates the lowest ratio (column-4) and the best ligand efficiency (column-6) with a very competitive binding energy (column-5). With a gross 11 atoms and 3 H atoms it offers 5 H bonds and astonishingly high 'inhibition constant' (relative to other APIs). Theoretically, it is the champion among our candidates. Practically, it is a small molecule. Also the least toxic (post infusion bearing wise). Antagonizes malignant cells more than the healthy. This is the oldest, most economic, surviving mass use versatile CT [20]. Yet clinically on mono use basis it is alleged as ineffective [21]. Why? a possible cause of becausing colossus waist of other APIs as FN (i) means feeble bond between F and N = swift

disassociation and unintended-uncontrolled rebonding (ii) antagonizes each & every cytokine. So? adjuvanting with Tipiracil or Trifluridine & maintaining the drug presence in blood (24x7) with non loading dosing plan posits helpful ~ is the critical distillate. Patients who were exposed to sub-clinical 5-Fu cyclically & the other two asyclically ranging over years are the living evidence of this low champion drug; ALSO excellent to restrain neo metastasis. Read with 'B'.

Row – D: Is a Natural, alkaloid from the bark of *Taxusbaccata*; Sister spp., Himalayan Yew\ *T wallichiana* (abundant). In-vivo it acts as a 'levy\tax' on the cell's [9]skeleton, debilitates it resulting in cell collapse (malignant-or-healthy). This is done by the 14 atoms of NO (ultra high concentration). It bio-accumulates in several off-target organs [22]. The at peak concentration of NO in blood can be 76 micro moles per 1 liter of body fluid. It has 14 atoms of NO = 2.3 moles\molecule which works out to many times in excess – hence anti-tissue activity of Taxens. Although 10 times heavier than 'C' its lipophilic property contributes to high 'inhibition constant' inspite of weak-ionic & low 'ligand efficiency'.

Row – E: Is a metallo-platinum API (platinum is the dominant part of the API). Is a story of the New ~ Pt is the new candidate. Pt isotope (1 atom per molecule) is conjugated with other atoms so as to lose its isotope form. Malignant cells's DNA express more guanine and cytosine and Pt has high affinity for these two nucleic acids; additionally with 75 electrons it offers a huge free energy gradient; forms optimum 3H bonds & binds well hence offers among the highest 'inhibition constant'. It has everything to be a champion. However, its whole physiology attacking toxicity is a failer. Why? because heavy metals (specially Pt) have equal affinity for healthy cells (API A-to-D have greater affinity for gone wrong cells). Pt remains deposited in whole body cells for a very long-long period, is deleterious for the whole physiology with recurrence, distance metastasis occurs invariably with a delayed action mechanism. Prognosis remains grave. In silico study yields a set of contrasting signatures for D than that of C. Table 3 suggests that formulators can help all stake holders by case specific astute fractional combinations of B-C-D-E[9].

In place of Pt, Fe can with ease be conjugated [23-25]. Fe conjugate use predate; has use history of more than a millennia as regenerative [26]. For *mammalian* malignancy therapeutics Fe is a wonderful option.

7.3. Supporting Info

Cancer therapy is convenient via IV route. B, C, D & E are IV members. They offer a gamut of atoms that addresses all the parameters to make a new therapy with known moieties. Due absence of confabulating, frail & heavy atoms B & C even with low ion content induces better super & para-magnetism [27] i.e., better ligand activity while D & Eare better for RBD and cytoplasm activity (red with Ref: 23-26). Co-administration at label dose is unbearable & full of consequences. Hence may prefer an amalgam @ fractional dose & no steroids, no ion inhibitors with each being administered separately immediate post its peak ½ blood life period. Drug Discoverers can take a cue as well have an opportunity to re-design; and manufacturers to re-package MDTs @ fractional doses. Table 3 is usefully talkative. Vis-à-vis metal-protein conjugate in mammalian therapeutics Fe compounds score well. They have been in use by Ayurveda for over a millennia (see Ref 18-20 & 35). FPs have a lot of observations on finger tips, hence should join 'Combat Cancer AT Home'. Either are peerless source for drug engineers.

7.4. Column Wise

The theoretical comparative docking exercise for all the API can be observed & studies in a scroll down manner.

Column 1: Generic names of 5 CT-APIs (A-to-E); A-to-C are pro-drugs that becomes a drug post metabolisation inside the body (mostly hepatic). D being a metal-protein conjugate wherein the metal moiety is Platinum (Pt) which is a near isotope (white metal); amino acid & O resistant. E is a plant toxoid, stable alkaloid with a rare NO moiety.

Column 2: Atomic composition & molecular weight. A-to-F use C-H-N-O-NO-FN-Pt atoms.

Column 3: Gives the number of 'heavy atoms' via-a-vis 'H' atom in the corresponding API.

Column 4: Gives the ratio of 'heavy atoms' via-a-vis 'H' atom. Such ratio does not create any rule for redacting any indication about 'binding energy', etc. Something else seems to be the influencing force or governor. Ratios are versatile.

Column 5: Gives the 'Binding Free Energy'\ 'theoretical Docking Score' between the ligand TNIK & the corresponding API. The greater the 'docking score' (e.g. 'B') the greater is the likelihood of the API binding to the TNIK.

Column 6: Gives the theoretical Ligand efficiency. It is a negative number. A large negative number points in the direction of better ligand efficiency. However, the small be the value the greater the chance of the API attacking healthy-&-cancer cells equally. In other words 'C' is likely to attach more to malignant cells while 'D' equally to all types.

Column 7: Inhibition Constant if all the 5 APIs.

Column 8: Gross number of atoms in each of the APIs.

Column 9: Of the gross number of atoms how many H Bonds are theoretically established in each of the APIs.

Column 10: Ratio between the gross number of atoms AND the number of H Bonds.

8. Discussion

Between all columns: There is an absence of even any suggestive talk about 'ion inhibitors' (that systemically\innately

[9] D' has to be a mini fraction (good) as at greater dose it will combine with Pt or with Fe & result in obstinate cellular deposits (bad); end of life stage palliative; non resectable locations; etc.

abound during CT cycles &\or triggered by APIs); 'peroxidase like activity'; RBD's hydrophobicity; API's lipophilic property; para magnetism; etc. HOWEVER Column wise consideration additionally makes Table 3 quite talkative in the sense that freak or supra conclusions viz., (i) linear (ii) [10]reverse (iii) reciprocal (iv) relationship cannot be established; cannot be drawn. This means (v) each API is unique (vi) uniqueness is picked up by the inSilico numerical matrix and held aloft as fractional number series i.e., sensitive series (vii) yields relevant comparative data in a capsule for stake holders. Worldwide, drugs are getting prescribed due to the grasp of the rapidly expanding user benefit by the stake holders [28].

8.1. Medico Legal Aspects

In India with 1.5 Billion poly-mix sub populations and an breathing legal system there are NO limitations on any clinician who is a Licensed Medical Practitioner under sub-section (1) of section 31 of the 'National Medical Commission Act – 2019'. She\He cannot be stopped from providing anti-cancer succor and\or practice chemo-therapy, etc. Furthermore, the same Act under Section 32, Sub Sections (1-to-3) provide for 'Community Health Providers' as real-time multi-disciplinary support. Such 'Community Health Provider's badge is open to all learned & involved stake holders - academics all fields [29]. British "Family Doctor Charter'-1966 [30] to Indian NMCA-2019 (the twin almost covers 1/3 of the global sub-populations) if be examined neither bans nor emphasizes a role for the rural or family physician in Cancer Combat in spite of the fact that they have a more intimate knowledge about the patient. Now some expouser about jargons shall help all stake holders specially to the bridge between referral centers and the Family Physicians and to the pharma-&-logistic industry.

8.2. Caveat

Our endeavours indicate that inSilico can possibly be used to engineer an API that will have a deep ¯ve Ki and a high ⁺veDk values. Such neo compound is likely to clinically result in (i) non toxic, no side effects, better tolerance (ii) small molecule (iii) enable continuous sub-clinical dosing (iv) long period – say 12-24 months CT at home engaging the Family Physician (& her\his local team) post master prescription from Apex-Referral centres = dispersion of patient under care model (v) macro domain benefit for all stake holders (vi) highly economic (vii) cold chain not requiring (viii) shelf-&-transhipment stable (vii) excellent therapeutic results i.e., progression arrest state (ix) no new metastasis (x) slow-&-smooth retraction ~ longer live well, profession enabling, event less, gradually receding, andexcellent anti-metastasis results (xi) steroid balm may get to be as unwarranted [10]. As opposed to our penta small molecules the Monoclonal Antibody (mAb {are single clones}). API formulations that are designed with very large mass; charge; affinity; gradient; Ki & Dk make a (A) different narrative (B) damage \ or\ bedeleterious for ligand's polygamy property.

9. Conclusion

For the same malady or cell-line treatment or for any clinical intervention alternative drugs are available. World-wide clinics are stressed pressed with most being one-person managed window. Should the clinician understand the jargons & the technical details then she\he can make a (deemed better) self evaluation from among the bio-similars & therapy similars that are available in the market. It takes patient centric care forward. Such effort gets to be lab-to-bed side. Lipinski's 5 coalesces the lengthy-&-complex bio-physics; chemistry; bio-chemistry; physics & mathematics into a few real-time quenched dynamic aspects (terms\jargons) to arrive at any 'likeness' (herein below). In cancer combat stake holders of all types do not understand the inputs that have gone into 'discovery', subsequent 'engineering', drug-dose regulatory calculation aspects of the drugs that are put to propaganda-marketed-prescribed-&-consumed. There is no focused document to refer to for in Silico jargons and that such dearth has become a bottleneck for the non initiated stake holders. It is a palpable crisis at levels. Amplification-simplification-with real time correlation is necessary. This communication provides a limited view of the deeply complex domainof the caption. Hence, there was a need to provide extra-mural support which have been set as '*notes*'. Is a baby step in a very essential direction and hence is nascent AND not exhaustive.

Abbreviations

API	Active Pharmaceutical Ingredient
CRC	Cancer of the Colon-to-rectum of the Elementary Canal
Cytokine	Inter cell & intra cell functions and medicines\functional foods functions & processes & services
Da	Dalton ~ a unit of volume: weight measure for molecules (medicines included).
DNA	Deoxyribonucleic Acid.
TNIK	T = tumor. N = necrosis. I = interacting. K= kinamatics
RAF	Rapidly Accelerated Fibrosarcoma

Author Contributions

Deepak Bhattacharya: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology

[10] Steroids (small molecule) precipitously downturn clinical side-effects & hard bearing aspects; also down-regulate the API's in-blood life inter-alia retain\up-regulate malignancy via a delayed action mechanism. Fractional chemo normally do not call for steroid balm.Oral steroid's ½ life being ~8hrs the Fluorine radical in steroids can easily antagonize\conjugate the APIs. Hence only the FP-&-Team are best placed to observe-monitor & apply.

Kavita Chanania: Resources, Software, Supervision, Validation

Chandra Sekhar Tripathy: Visualization, Writing – original draft, Writing – review & editing

Conflicts of Interest

The authors declare no conflicts of interest.

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