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Cancer, Cytologism and the Kinase Inhibitors Saga

Andras Paldi[a] *& Carlos Sonnenschein*[b*]

[a] *Ecole Pratique des Hautes Etudes PSL Research University Paris France*
[b] *Tufts University School of Medicine, Boston, MA USA*

***Corresponding author:** Carlos Sonnenschein, Email: carlos.sonnenschein@tufts.edu

Abstract

The role of kinases in the cell cycle of unicellular eukaryotes and cells of multicellular organisms has been the object of numerous studies involving normal and cancer cells. These studies described in detail how two daughter cells are ge-nerated from a single normal or cancer mother cell. Among the thousands of participants in the cell cycle, kinases play a crucial role in the dynamic aspects of the cell cycle thanks to the phosphorylation of substrates with which they react. Inhibitors of these kinases have figured prominently among the strategies to treat cancers. However, evidence shows that the benefits that cancer patients accrued from this therapeutic approach have been of a limited degree. In this arti-cle, we review the rationale for adopting such a strategy and the factors that contribute to its shortcomings.

Keywords: cancer, somatic mutation theory, tissue organization field theory, tyrosine kinases, kinase inhibitors, cell cycle, carcinogenesis

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1. Introduction

The proliferation of somatic cells in multicellular organisms is accomplished through a rather strictly regulated process called the cell cycle (Alberts *et al.* 2014; Weinberg 2014). The completion of the cell cycle in somatic cells of multicellular organisms takes a variable amount of time during which those cells traverse four stages arbitrarily called G0/G1 (G stands for gap), S (S stands for DNA synthesis), G2 and M (M stands for mitosis). Consistently, at the end of the cell cycles a "mother" cell generates two similar but not identical "daughter" cells. These stages occur regardless of whether the cells are normal or neoplastic (Nurse 1990).

The description of the myriad of molecular/biochemical interactions taking place during the cell cycle in cells from multicellular organisms has clarified to a great extend *how* cells accomplish their reproductive function. Those steps are not much different from those happening in unicellular eukaryotes, like yeast (Rew and Wilson 2000; Alberts *et al.* 2014). In fact, the characterization of those steps in yeast have enriched the detailed roles played by the cell cycle components in cells of multicellular organisms regardless, again, of whether those cells were of normal or cancer origin. Intriguingly, however, textbooks of both normal and cancer cell biology, as well as research papers in these areas have claimed for several decades that the signaling pathways happening during the cell cycle in cancer cells are qualitatively altered when compared with those in normal cells (Hunter 1998; Blume-Jensen and Hunter 2001). More specifically, under the notion that there are qualitative differences between the cell cycles of normal somatic cells and their cancerous counterparts, it has been widely reported that cyclin-dependent kinase (CDK) dysregulation, directly or indirectly, plays

an essential role in carcinogenesis (Malumbres and Barbacid 2009). In addition, this notion that cyclin-dependent kinase (CDK) dysregulation underlie other diseases has not been restricted to the carcinogenesis area alone: comparable views regarding altered intracellular signaling processes involving kinases have been extended to virtually all major diseases, such as immunological, inflammatory, degenerative, metabolic, cardiovascular, infectious diseases, epilepsis, and even mental retardation (Ferguson and Gray 2018; Maury *et al.* 2024).

All along, it has been reported that there are anywhere between 518 and over a thousand kinases encoded in the human genome that are responsible for the phosphorylation of a third of its proteome. As a result, the ubiquity of kinases makes testing the specific role of each of those mutated enzymes singly or in combination a challenging task. However, empirical evidence indicates that, either singly or in combination, mutated kinases do not deleteriously influence cell cycle steps to the extent that can be empirically verified downstream through altered cell counts when compared with non-mutated cells (Rew and Wilson 2000).

In addition, although it is seldom mentioned explicitly, the rationale behind aggressively studying the cell cycle of somatic cells and the role of kinases in it relates to the two assumptions on which the somatic mutation theory of carcinogenesis (SMT) is based, namely, 1) cancer is a cell-based disease, and 2) carcinogenesis is due to an accumulation of somatic mutations in a multitude of genes, included those involved in intracellular signaling, in an initially normal somatic cell that eventually due to the intracellular disruptions caused by those mutations will generate a neoplasm. Due to multiple incongruencies (Soto and Sonnenschein 2020; Sonnenschein and Soto 1999), the SMT has been the object of multiple course-corrections (see below). As with other intracellular molecular targets (genes, transcriptional and translational components) (De Magalhães 2022), and structural organelles (mitochondria, nucleolus, chromosomes), kinases have also been singled out as prominent targets of carcinogens and therefore, as a result of this assumed interaction, a consensus in this field adopted the notion that they are responsible for the unwieldy behavior of cancer cells. Based on this inference, it was concluded that kinase inhibitors (KIs) represented promising therapeutic agents for cancer patients (Suski *et al.* 2021). It is noteworthy, however, that first, normal cells can proliferate as fast or even faster than cancer cells; examples of rapidly proliferating normal cells are those following egg fertilization, cells in the epithelium of the intestinal tract, and hematopoietic cells. Second, mutated cell cycle kinases do not show distinctive proliferative phenotypes. And third, the original argument proposing that KIs exert their therapeutic effects by targeting mutated kinase-coding genes (BCL/etc translocation) has been subject to criticism based on the acknowledged argument that therapeutic drugs (for cancer and other diseases) have pleiotropic effects, a feature that prevents assigning accurate causation to these drugs. Separately, statistical analysis of the effects of cancer treatment in the last decades suggest that aggressive efforts in this direction have not significantly affected the overall survival of cancer patients (Unni and Arteaga 2019; Settleman *et al.* 2018; Carlisle *et al.* 2020; Tiwari *et al.* 2024).

2. KIs in Cancer Therapy

For several decades now, based on the previously mentioned idea that there are qualitative differences in the signaling pathways utilizing kinases in general and more specifically those of the cell cycle of normal and cancer cells, most cancer researchers agreed with the notion that KIs should occupy a prominent role in the strategy to effectively treat the disease. To develop such a therapeutic strategy, researchers concentrated on two main areas: a) one aimed at strictly defining the biochemical and biophysical properties of those enzymes (Hunter 1998; Blume-Jensen and Hunter 2001; Mortuza *et al.* 2018), and b) another one aimed at examining the roles of kinases in functional cellular events which affect the dynamics of the cell cycle and how to deal with alleged kinase malfunctions (Suski *et al.* 2021; Besson *et al.* 2008).

Finding small size KIs to use as therapeutic tools has been intensively pursued for a period long enough to allow for a fair evaluation of the outcome of this strategy (Prasad 2020). In fact, many compounds initially reported to be therapeutically effective were subsequently shown to lack potency, selectivity and/or be toxic (Goel *et al.* 2018; Jiang *et al.* 2023; Tiwari *et al.* 2024).

The lack of significant benefits from this therapeutic approach invites the proposal of alternative plausible explanations to either refine, if possible, the unproductive strategy, or else to abandon it altogether if proven ineffective or damaging to the patient's wellbeing. To further explore the subject, we focused our attention on i) the epistemology of carcinogenesis and ii) the rationale of designing the therapeutical approaches aimed at effectively "curing" or, at least, arresting the progress of this disease.

Table 1: Control of cell proliferation in the context of theories of carcinogenesis.

	The somatic mutation theory (SMT)	***The tissue organization field theory (TOFT)***
Implicit premise	Default state: *quiescence*	----------
Explicit premises		Default state: *proliferation*
	Neoplasms due to mutations in cell cycle and cell proliferation regulatory genes	
	Proliferation stimulated by exogenous growth factors	Proliferation controlled by exogenous and endogenous inhibitory factors
	Cell cycle is affected by oncogenes, suppressor genes, cyclins, inhibitory factors	
	Carcinogenesis occurs at the cellular level of biological organization	Carcinogenesis occurs at the tissue level of biological organization (tissue-tissue interactions)
	Control of cell proliferation and control of the cell cycle are often conflated	
	Neoplasms are monoclonal	
Corollary	Cancer is irreversible	Cancer is reversible

3. Cancer theories

Currently, there are two main theories of carcinogenesis. They are: i) the still hegemonic cell-based SMT proposed by Theodor Boveri in 1914 and ii) the Tissue Organization Field Theory (TOFT) proposed in 1999 (Sonnenschein and Soto 1999). Of note, the TOFT differs from the SMT in two fundamental criteria; first, while the SMT assumes that the default state of cells in multicellular organisms is *quiescence*, the TOFT explicitly posits instead that *proliferation* is the default state of *all* cells (Shomar *et al.* 2022). And second, while the SMT considers cancer a *cell-based* disease, the TOFT considers it as a *tissue-based* one (Table 1). Empirical evidence generated over the years when applying the strategy promoted by the SMT (i.e., cell killing, inhibition of cell proliferation) encountered multiple examples of lack of fit. When addressing these inconsistencies, researchers siding with the SMT incorporated course corrections to this theory's original version (Sonnenschein and Soto 2020). Among them, the microenvironment surrounding the original "normal" cell was added as a supplemental target that also accumulated somatic mutations or affected cancer epithelial cells through epigenetic modifications. This *ad hoc* course correction represent a "compromise" involving the original SMT plus the role played in this instance by the stroma that surrounds the primary epithelial tumor cells; this alternative was already proposed in the 1930s by J. Needham and by C. Waddington. Altogether, despite the incorporation of this and other theoretical manipulations as add-ons to the SMT, these "compromises" retain the assumption of a causal carcinogenic role for the somatic mutations accumulated in normal epithelial cells that eventually may become neoplastic (while generating mostly carcinomas). Essentially, regardless of which of these *ad hoc* modifications is adopted, the consensus that cancer is a *cell-based*, genetic, molecular disease remains unaltered. Interestingly, these conclusions are still considered meritorious by most cancer researchers even when it has been reproducibly shown that clones of normal cells present in several organs that will not generate cancers carry alleged cancer-causing "driver" mutations and that "cancer cells" that are part of a neoplasia do not carry those same "driver" mutations (Martincorena and Campbell 2015; Dou *et al.* 2018; Martincorena *et al.* 2018; Kakiuchi and Ogawa 2021). The incorporation of novel powerful and less expensive sequencing technologies resulting from the significant contributions of the Molecular Biology Revolution has contributed to unexpectedly clarify that the genome of normal cells carried comparable cancer "driver" gene mutations to those thought to be unique to cancer cells (Martincorena and Campbell 2015; Dou *et al.* 2018; Martincorena *et al.* 2018; Kakiuchi and Ogawa 2021). If anything, as pointed out above, the data now collected through deep sequence probes suggest instead that those alleged cancer-causing "driver" mutations are also present in cells which are considered normal (meaning non-cancer cells) (Naxerova 2021; Colom *et al.* 2021). This new development justifies K. Naxerova's pondering: "These new insights invite us to reconsider how we genetically define cancer. If having multiple driver mutations does not make a cancer, what does?".

4. Cell Proliferation and Effective KI Activity in Cancer Therapy

Toward the end of last century, aberrant tyrosine phosphorylation was being considered as an important hallmark in cancer initiation (Hunter 1998). The expected effectiveness of KIs was predicated on a series of inferences that supported the rationale that these drugs would have selectively slowed down the speed of the cell cycle of cancer cells. Those expectations have not been fulfilled as anticipated because, among other reasons, a lack of specificity. Separately, after two decades of insisting that the core of the carcinogenic event can be attributed to a dysregulation of the cell cycle of cancer cells due to "either overexpression of cyclin D1, loss of p16Ink4a, the mutation of CDK4 to an Ink4-refractory state, or the loss of Rb itself", no plausible alternatives in the form of novel KIs are being offered by academic research or BigPharma labs. Notwithstanding, all along, the notion that cell cycle signaling defects in cancer cells are central to the difference between normal and cancer cells is still being promoted (Classon and Harlow 2002; Klein *et al.* 2018; Prasad 2016; Naxerova 2021; Colom *et al.* 2021).

During a standard human lifetime, it is estimated that the average person will undergo about 10^{14} cell cycles in an uneven timescale. That is, some cells in some tissues proliferate during embryonal, fetal, and early childhood and then enter a period during which proliferation is rather minimal or totally absent (neurons, fibroblasts, etc.; meanwhile, cells in other tissues proliferate incessantly (bone marrow, intestinal system, skin). Simultaneously, epithelial cells in other organs of metazoans proliferate at different speeds while moving (streaming) and expressing their "differentiated" functions. So called "differentiated" cells are continuously subject to changes in their respective local morphogenetic units and other changes imposed on them by extemporaneous homeostatic conditions, e.g. – adult stem cell trans-differentiation. In other words, under physiological conditions, cells performing "specialized" functions (such as hepatocytes secreting albumin, small intestine epithelial cells absorbing nutrients, epithelial cells in glandular organs secreting milk, saliva, enzymes, etc.) nonetheless do continue to proliferate and move unperturbed. This uncontested feature implies that there is no obligatory linkage between the ability of cells to proliferate and move on the one hand, and the ability of those same cells to concurrently synthesize and/or secrete a variety of cell products (collagen, albumin, sex hormones, etc.), on the other (Sonnenschein and Soto 2021).

As summarized above, kinases have been claimed to be causally involved in the carcinogenic process. Based on this premise emerged the notion of small molecular KIs as a potentially powerful class of effective drugs in cancer therapy (Ferguson and Gray 2018; Zhou *et al.* 2016). How can the discrepancy between promising pre-clinical effects and the lack of equivalent results in clinical tests be explained? In addition to the lack of specificity argument allude to above, several possible explanations were proposed by the defenders of the "kinase inhibitor" therapeutic strategy. Recently, pioneers in this field conceded that dozens of published articles on a leucine zipper-containing serine/threonine kinase called MELK lacked credibility (Settleman *et al.* 2018). It was also claimed that MELK is activated during the cell cycle and is important for maintaining proper asymmetric division of stem cells (Ganguly *et al.* 2015). As a result of this inference, kinases were then considered worthy, potential therapeutic targets in human cancers. However, researchers recently claimed that the experimental criteria used to validate candidate cancer therapeutic targets was subject to serious methodological faults (Settleman *et al.* 2018). The main factors responsible for the credibility gap were considered technical, namely, the use of cancer cells in culture conditions or the use of RNA interference for target validation. Notwithstanding, it is equally plausible that additional technical factors contribute to the failure to validate the candidate kinase inhibitors. Off-target deleterious effects of TKs could be considered as valid explanations for the therapeutic failures (Gyawali *et al.* 2021).

At first glance, off-target effects and poor selectivity may appear as an issue of poor inhibitor design and/or unanticipated pleiotropy of action. For example, while the expression level of the above-mentioned MELK has been strongly correlated with the mitotic activity in human cancers and remains one of the main predictors of the patient mortality in a variety of tumors, cancer cells with a loss-of-function MELK mutation still proliferate at wild-type levels. In addition, the known targets of MELK also become phosphorylated in these cells. This and similar examples of the lack of biological specificity of alleged chemically specific enzyme inhibitors illustrate the difficulty of achieving a selective effect by targeting redundantly acting enzymes. Beyond the practical implications, functional redundancy casts doubt on the possibility that a single mutation in a single kinase gene by itself may induce cancer. The initial

enthusiasm generated by biochemists and molecular biologists for the specificity of KIs obscured the concept of redundancy and pleiotropy omnipresent in living organisms.

Inhibitors of essential kinases represent another example of the difficulty of achieving biologically selective effects using high-potency enzyme inhibitors. This difficulty is conceptual and not just technical. The development of mitotic kinase inhibitors was based in part on the idea that targeting only cycling cells will minimize the toxicity on post-mitotic cells. Unfortunately, these inhibitors lack an effective therapeutic window because of the high toxicity observed on non-neoplastic tissues with a high cellular proliferation rate exposed to KIs (Zhou *et al.* 2016). As explained above, it is a common misconception that cancer cells proliferate more rapidly than cells in normal tissues. Also, as mentioned above, several normal tissues have higher proliferation rates than most tumors. Proliferating cells in these normal tissues are also targeted and affected by KIs.

Another example illustrating the confusion between conceptual and technical difficulties is provided by the inhibitors of PI3K kinases (Vasan and Cantley 2022). PI3Ks are involved in a wide variety of pathways linked to cell growth, proliferation and differentiation through their role in the regulation of metabolic and insulin pathways. This class of kinases were and still are considered as potential candidates for therapy. Several drugs targeting the PI3K pathway have received approval. However, as in all other cases with KIs, achieving a therapeutic window that maximizes efficacy and minimizes adverse effects has proven to be a major barrier to an effective therapeutic use of Pl3K inhibitors (Prasad 2020; Tiwari *et al.* 2024).

5. Conclusions

The example of kinase inhibitors highlights how the systematic use of *ad-hoc* explanations to account for unexpected results may hide important conceptual problems that eventually canalize the research into dead-ends. The failure of kinase inhibitors as effective anti-cancer drugs challenges first, the decades-old assumption that cancer is a *cell-based* disease as suggested by the SMT. And second and of comparable, if not greater importance, the failure of those therapeutic approaches aimed at correcting those proposed, but yet-to-be rigorously documented cell cycle signaling defects, obscures productive avenues aimed at both preventing carcinogenesis and to offer effective therapeutic options based on alternative theoretical approaches. These shortcomings were already noticed over 60 years ago by David Smithers who, based on rigorous clinical data he collected, offered an organicist-based alternative to the cytologism that then began to dominate experimental and clinical cancer research (Soto and Sonnenschein 2020). Additional evidence accumulated since then -4point to the need to switch attention to theoretical and empirical alternatives that, as the TOFT proposes, are based on solid evolutionary-based premises, such as those related to the default state of cells and the merits of considering cancer as a *tissue-based* disease.

The rationale of remaining loyal to a thoroughly mistaken theory and to the diagnostic, prognostic and therapeutic mishaps that have followed as a result, does not benefit the wellbeing of cancer patients or the prestige of the scientific enterprise. Abandoning the SMT and its wrongheaded implications over cancer diagnoses and therapies is long overdue (Sonnenschein and Soto 2000).

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References

Alberts, B, Johnson, A, Lewis, J, Morgan, D, Raff, M, Roberts, K, & Walter, P 2014, *Molecular Biology of the Cell*, Garland Science, New York.

Besson, A, Dowdy, SF, & Roberts, JM 2008, "CDK inhibitors: cell cycle regulators and beyond", *Dev Cell*, 14, pp. 159-69.

Blume-Jensen, P, & Hunter, T 2001, "Oncogenic kinase signalling", *Nature*, 411, pp. 355-365.

Carlisle, BG, Zheng, T, & Kimmelman, J 2020, "Imatinib and the long tail of targeted drug development", *Nat Rev Clin Oncol*, 17, pp. 1-3.

Classon, M, & Harlow, E 2002, "The retinoblastoma tumour suppressor in development and cancer", *Nat Rev Cancer*, 2, pp. 910-917.

Colom, B, Herms, A, Hall, MWJ, Dentro, SC, King, C, Sood, RK, Alcolea, MP, Piedrafita, G, Fernandez-Antoran, D, Ong, SH, Fowler, JC, Mahbubani, KT, Saeb-Parsy, K, Gerstung, M, Hall, BA, & Jones, PH 2021, "Mutant clones in normal epithelium outcompete and eliminate emerging tumours", *Nature*, 598, pp. 510-514.

De Magalhães, JP 2022, "Every gene can (and possibly will) be associated with cancer", *Trends Genet*, 38, pp. 216-217.

Dou, Y, Gold, HD, Luquette, LJ, & Park, PJ 2018, "Detecting Somatic Mutations in Normal Cells", *Trends Genet*, 34, pp. 545-557.

Ferguson, FM, & Gray, NS 2018, "Kinase inhibitors: the road ahead", *Nat Rev Drug Discov*, 17, pp. 353-377.

Ganguly, R, Mohyeldin, A, Thiel, J, Kornblum, HI, Beullens, M, & Nakano, I 2015, "MELK-a conserved kinase: functions, signaling, cancer, and controversy", *Clin Transl Med*, 4, p. 11.

Goel, S, Decristo, MJ, Mcallister, SS, & Zhao, JJ 2018, "CDK4/6 Inhibition in Cancer: Beyond Cell Cycle Arrest", *Trends Cell Biol*, 28, pp. 911-925.

Gyawali, B, Rome, BN, & Kesselheim, AS 2021, "Regulatory and clinical consequences of negative confirmatory trials of accelerated approval cancer drugs: retrospective observational study", *Bmj*, 374, p. n1959.

Hunter, T 1998, "The Croonian Lecture 1997. The phosphorylation of proteins on tyrosine: its role in cell growth and disease", *Philos Trans R Soc Lond B Biol Sci*, 353, pp. 583-605.

Jiang, M, Gu, D, Liu, F, Lin, C, & Tian, L 2023, "Transforming cancer cells for long-term living with cancer: An inspiring new approach", *Chin J Cancer Res*, 35, pp. 108-125.

Kakiuchi, N, & Ogawa, S 2021, "Clonal expansion in non-cancer tissues", *Nat Rev Cancer*, 21, pp. 239-256.

Klein, ME, Kovatcheva, M, Davis, LE, Tap, WD, & Koff, A 2018, "CDK4/6 Inhibitors: The Mechanism of Action May Not Be as Simple as Once Thought", *Cancer Cell*, 34, pp. 9-20.

Malumbres, M, & Barbacid, M 2009, "Cell cycle, CDKs and cancer: a changing paradigm", *Nat Rev Cancer*, 9, pp. 153-166.

Martincorena, I, & Campbell, PJ 2015, "Somatic mutation in cancer and normal cells", *Science*, 349, pp. 1483-1489.

Martincorena, I, Fowler, JC, Wabik, A, Lawson, ARJ, Abascal, F, Hall, MWJ, Cagan, A, Murai, K, Mahbubani, K, Stratton, MR, Fitzgerald, RC, Handford, PA, Campbell, PJ, Saeb-Parsy, K, & Jones, PH 2018, "Somatic mutant clones colonize the human esophagus with age", *Science*, 362, pp. 911-917.

Maury, EA, Walsh, CA, Kahle, KT 2024, "Neurosurgery elucidates somatic mutations", *Science*, 10.1126/science.adj2244.

Mortuza, GB, Hermida, D, Pedersen, AK, Segura-Bayona, S, López-Méndez, B, Redondo, P, Rüther, P, Pozdnyakova, I, Garrote, AM, Muñoz, IG, Villamor-Payà, M, Jauset, C, Olsen, JV, Stracker, TH, & Montoya, G 2018, "Molecular basis of Tousled-Like Kinase 2 activation", *Nat Commun*, 9, p. 2535.

Naxerova, K 2021, "Mutation fingerprints encode cellular histories", *Nature*, 597, pp. 334-336.

Nurse, P 1990, "Universal control mechanism regulating onset of M-phase", *Nature*, 344, pp. 503-508.

Prasad, V 2016, "Perspective: The precision-oncology illusion", *Nature*, 537, p. S63.

Prasad, V 2020, *Malignant*, Johns Hopkins University Press, Baltimore (Maryland).

Rew, DA, & Wilson, GD 2000, "Cell production rates in human tissues and tumours and their significance. Part II: clinical data", *Eur J Surg Oncol*, 26, pp. 405-417.

Settleman, J, Sawyers, CL, & Hunter, T 2018, "Challenges in validating candidate therapeutic targets in cancer", *Elife*, 7.

Shomar, A, Barak, O, & Brenner, N 2022, "Cancer progression as a learning process", *iScience*, 25, p. 103924.

Sonnenschein, C, & Soto, AM 1999, *The Society of Cells: Cancer and Control of Cell Proliferation*, Springer Verlag, New York.

Sonnenschein, C, & Soto, AM 2000, "The somatic mutation theory of carcinogenesis: Why it should be dropped and replaced", *Molecular Carcinogenesis*, 29, pp. 1-7.

Sonnenschein, C, & Soto, AM 2020, "Over a century of cancer research: Inconvenient truths and promising leads", *PLoS Biol.*, 18, p. e3000670.

Sonnenschein, C, & Soto, AM 2021, "Control of cell proliferation: is the default state of cells quiescence or proliferation", *Organisms*, 5, pp. 33-42.

Soto, AM, & Sonnenschein, C 2020, "Revisiting D.W. Smithers's 'Cancer: An Attack on Cytologism' (1962)", *Biological Theory*, 15, pp. 180-187.

Suski, JM, Braun, M, Strmiska, V, & Sicinski, P 2021, "Targeting cell-cycle machinery in cancer", *Cancer Cell*, 39, pp. 759-778.

Tiwari, A, Kumari, B, Nandagopal, S, Mishra, A, Shukla, KK, Kumar, A, Dutt, N, Ahirwar, DK 2024, "Promises of Protein Kinase Inhibitors in Recalcitrant Small-Cell Lung Cancer: Recent Scenario and Future Possibilities", *Cancers*, 16, p. 963. https://doi.org/10.3390/cancers16050963.

Unni, N, & Arteaga, CL 2019, "Is Dual mTORC1 and mTORC2 Therapeutic Blockade Clinically Feasible in Cancer?", *JAMA Oncol*, 5, pp. 1564-1565.

Vasan, N, & Cantley, LC 2022, "At a crossroads: how to translate the roles of PI3K in oncogenic and metabolic signalling into improvements in cancer therapy", *Nat Rev Clin Oncol*, 19, pp. 471-485.

Weinberg, RA 2014, *The Biology of Cancer*, Garland Science, New York.

Zhou, Y, Shen, JK, Hornicek, FJ, Kan, Q, & Duan, Z 2016, "The emerging roles and therapeutic potential of cyclin-dependent kinase 11 (CDK11) in human cancer", *Oncotarget*, 7, pp. 40846-40859.