Bioelectric Pharmacology of Cancer: A Meta-Analysis of Ion Channel Drugs Affecting the Cancer Phenotype

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Abstract

Cancer is a pernicious and pressing medical problem; moreover, it is a failure of multicellular morphogenesis that sheds much light on evolutionary developmental biology. Numerous classes of pharmacological agents have been considered as cancer therapeutics and evaluated as potential carcinogenic agents. Here, we briefly review recent work on ion channel drugs as promising anti-cancer treatments and present a meta-analysis of the cancer-relevant effects of 109 drugs targeting ion channels. The roles of ion channels in cancer are consistent with the importance of bioelectrical parameters in cell regulation and with the functions of bioelectric signaling in morphogenetic signals that act as cancer suppressors. We find that compounds that are well-known for having targets in the nervous system, such as voltage-gated ion channels, ligand-gated ion channels, proton pumps, and gap junctions are especially relevant to cancer. Our analysis suggests further opportunities for the repurposing of numerous promising candidates in the field of cancer electroceuticals.

Introduction

Cancer refers to a constellation of disorders in which cells begin to proliferate, migrate, and signal in ways that are not adaptive for the whole organism (Rubin 1985; Rubin et al. 1996; Sonnenschein et al. 2014; Thomas et al. 2016; Gatenby 2017; Levin 2021b). This often involves metastasis, with tumor cells travelling through blood or the lymphatic system to invade nearby or distant tissues. Overall, it is the second leading cause of death in the United States (Siegel et al. 2023). The American Cancer Society projects that ~1.9 million cases of cancer will be diagnosed in 2023, with greater than half a million deaths (Siegel et al. 2023). It is estimated that 19.3 million new cancer cases were diagnosed worldwide in 2020, with cancer estimated to be responsible for one in every six deaths (Debela et al. 2021).

Current cancer treatments focus on approaches such as surgical tumor excision, chemotherapy, and radiotherapy. These aim to eliminate and destroy the tumor and its cells. Immunotherapy is also a highly active field of research (Kennedy and Salama 2020; Dong et al. 2021; Zhao et al. 2023). Despite the massive efforts devoted to this problem for the last six decades, the prospects for cancer patients are still far from satisfactory (Abernethy et al. 2014; Jaffee et al. 2017; Dong et al. 2019), due to the side effects of current drugs and the phenomenon of drug resistance in cancer (Liscovitch and Lavie 2002; Liu 2009; Di and Zhao 2015; Mansoori et al. 2017; Saha and Lukong 2022). It is widely understood that alternative approaches and paradigms are required to improve cancer biomedicine.

The fundamental nature of cancer has been approached from many perspectives, focusing on diverse aspects such as microenvironment, genomic damage, stress, game theory of cooperation and competition among cells, evolutionary processes, and disorders of multicellularity (Kenny et al. 2007; Tarin 2012b; Tarin 2012a; Shiozawa et al. 2013; Tarin 2013; Sonnenschein and Soto 2015; Wu et al. 2015; Sonnenschein and Soto 2016; Stankova et al. 2018; Valkenburg et al. 2018; Amend et al. 2019; Archetti and Pienta 2019; Jacques et al. 2022; Truskowski et al. 2023). One critical aspect is the breakdown of the normal mechanisms that keep individual cells harnessed toward large-scale anatomical goals - the maintenance of complex tissues and organs – and a reversion to ancient unicellular behavioral policies (Rubin 1985; Lineweaver et al. 2014; Davies and Agus 2015; Bussey et al. 2017; Cisneros et al. 2017; Levin 2019). Thus, a solution to cancer is likely to involve modulation of the mechanisms that establish and maintain collective order in vivo. One major mechanism underlying this is endogenous bioelectricity (Figure 1) (Chernet and Levin 2013a; Bates 2015; Levin 2021b).

All cells, not just neurons, communicate electrically, using ion channels and electrical synapses known as gap junctions to establish spatio-temporal patterns of resting potential and ion flow within tissues (Harris 2021; Funk and Scholkmann 2023). These gradients underlie the collective anatomical decision-making of organs and tissues, being central regulators of growth and form during regeneration and development (Levin 2021a) – two

processes of central relevance to cancer (Wolsky 1978; Pierce 1983; Pierce et al. 1986; Brockes 1998; Oviedo and Beane 2009). Modulation of bioelectric state using drugs, ion channel mutations, and optogenetic light stimuli has been shown to prevent and normalize tumors in animal models (Lobikin et al. 2012; Chernet and Levin 2013a; Chernet and Levin 2013b; Chernet and Levin 2014; Chernet et al. 2015; Chernet et al. 2016). It is thus not surprising that ion channels are being identified as oncogenes, and ion channel drugs are increasingly seen as cancer drug candidates (Arcangeli et al. 1995; Fraser et al. 2000; Djamgoz et al. 2001; Krasowska et al. 2004; Onganer and Djamgoz 2005; Isbilen et al. 2006; Brackenbury and Djamgoz 2007; Uysal-Onganer and Djamgoz 2007; Ding et al. 2008; Diss et al. 2008; Palmer et al. 2008; Arcangeli et al. 2009; Onkal and Djamgoz 2009; Arcangeli and Becchetti 2010; Fraser et al. 2010; Restrepo-Angulo et al. 2010; Becchetti 2011; Arcangeli et al. 2012; Frede et al. 2013; Lansu and Gentile 2013; Fairhurst et al. 2014; Fraser et al. 2014a; Fraser et al. 2014b; Kale et al. 2015; Nelson et al. 2015a; Nelson et al. 2015b; Perez-Neut et al. 2015a; Perez-Neut et al. 2015b; Rao et al. 2015; Fairhurst et al. 2016; Gentile 2016; Mohammed et al. 2016; Becchetti et al. 2017; Fukushiro-Lopes et al. 2018; Breuer et al. 2019; Altamura et al. 2022; Capatina et al. 2022; James et al. 2022; Mathews et al. 2022; Zuniga et al. 2022; Fairhurst et al. 2023).

Ion channels are essential for a myriad of physiological processes, including but not limited to heart contraction, nerve signal transmission, temperature sensation, hormonal release, and apoptotic regulation. Among other related functions, ion channels are known to maintain cell membrane potential and participate in signal transduction. Importantly, ion channels have been found to be key regulators in cancer pathophysiology, working in concert with multifaceted roles from initial cancer transformation to metastasis (Arcangeli et al. 2009; Arcangeli and Becchetti 2010; Restrepo-Angulo et al. 2010; Becchetti 2011; Kale et al. 2015; Altamura et al. 2022; Capatina et al. 2022; Mathews et al. 2022; Zuniga et al. 2022). Differential ion channel expression coincides with specific stages of cancer, including modulation of cell proliferation, apoptosis, metastasis/invasion and spread (Arcangeli et al. 2009). A wide variety of K^+, Cl^-, Ca^{2+} and Na^+ channels play a significant role in different stages of cancer development, including cancer cell resistance to chemotherapy (Arcangeli et al. 2012; Altamura et al. 2022).

Importantly, while dysfunctional potassium channels have been found to lead to a cancer phenotype or govern cell state (Arcangeli et al. 1995; Becchetti et al. 2017; Zuniga et al. 2022), upregulation or activation of potassium channels (including hERG channels) has been shown to reduce metastasis and cancer (Lansu and Gentile 2013; Perez-Neut et al. 2015a; Perez-Neut et al. 2015b; Rao et al. 2015; Gentile 2016; Fukushiro-Lopes et al. 2018; Breuer et al. 2019). Similarly, while voltage-gated sodium channels are expressed in a wide variety of carcinomas, inhibitory drugs targeting these channels reduced cancer and metastasis (Fraser et al. 2000; Djamgoz et al. 2001; Krasowska et al. 2004; Onganer and Djamgoz 2005; Isbilen et al. 2006; Brackenbury and Djamgoz

2007; Uysal-Onganer and Djamgoz 2007; Ding et al. 2008; Diss et al. 2008; Palmer et al. 2008; Onkal and Djamgoz 2009; Fraser et al. 2010; Fairhurst et al. 2014; Fraser et al. 2014a; Fraser et al. 2014b; Nelson et al. 2015a; Nelson et al. 2015b; Fairhurst et al. 2016; Mohammed et al. 2016; James et al. 2022; Fairhurst et al. 2023). Because of their importance in setting and maintaining voltage gradients and their involvement in neoplastic conversion, ion channels are promising targets for cancer therapy and have been studied for the development of anti-cancer medicines (Fraser et al. 2000; Arcangeli et al. 2009; Arcangeli and Becchetti 2010; Arcangeli et al. 2012; Fairhurst et al. 2014; Kale et al. 2015; Nelson et al. 2015a; Fairhurst et al. 2016; Mohammed et al. 2016; Becchetti et al. 2017; Capatina et al. 2022; Zuniga et al. 2022; Fairhurst et al. 2023). We have argued that repurposing ion channel-modulating drugs already used in human patients may provide a timely, safe, and cost-effective strategy for discovering novel therapeutics (Kale et al. 2015; Pio-Lopez and Levin 2023). To facilitate the discovery of candidates, here we provide the results of a meta-analysis that mined the literature for connections between known drugs and the cancer phenotype.

Methods

Our methodology for the meta-analysis consisted of the following steps:

Literature Search Strategy

The search began with the data in the IUPHAR Guide to Pharmacology Website (Harding et al. 2022), where we viewed the complete list of Ion Channels, including Ligand-Gated Ion Channels, Voltage-Gated Ion Channels, TRP superfamily, and Other Ion Channels. Beside each Ion Channel, we used IUPHAR to create a list of all the drugs that are Antagonists, Selective Antagonists, and Channel Blockers, Activators of the specific ion channel, combining subunits into one ultimate list. In parallel, DrugBank [38] was accessed using the keyword “Ion Channel” resulting in a list of drugs that affect ion channels. The search also included Proton Pump Inhibitors, using (Robinson and Horn 2003) and Gap Junction Blockers using (Manjarrez-Marmolejo and Franco-Perez 2016). In certain cases, drugs were listed as targeting one particular ion channel, but are also known to have another biochemical mechanism of action or target. This was noted accordingly in Tables 1,2, and X.

Selection of Relevant Studies and Criteria

After compiling a master list of ion channel drugs organized by primary target, we assessed each drug from the list and categorized its effects to be either cancer or anti-cancer after conducting a literature search. We typed keywords “*Drug Name*, carcinogen” and “*Drug Name*, cancer” in the Title/Abstract or Abstract/Abstract categories respectively of PubMed or Clarivate EndNote search tool. Our meta-analysis

additionally identified drugs that did not primarily target ion channels, yet affected them as side targets (Table 3).

Based on these search results, we classified each drug into the categories Yes, No or Unclear, as follows (Figure 2):

- Yes – at least one article/study described a carcinogenic or anti-cancer effect of the drug. For the "Carcinogenic" table (Table 1), the drug of interest increased cancer cell proliferation, increased incidence of carcinoma/cancer, promoted tumorigenesis, etc. In some cases, a metabolite of the drug was a known carcinogen, which was noted in the Tables. For the "Anti-cancer" table (Table 2), the drug of interest reduced proliferation of cancer cells, slowed down tumor progression, or was successfully implemented in a therapeutic strategy. For the Drugs with off-target effect on ion channel (Table 3), a relationship was found between the drug of interest and cancer, but the ion channel was not the primary target. Within each table, drugs were categorized into groups depending on which ion channel family was targeted. Ion channel families are listed in alphabetical order. Within each ion channel family category, drugs are also listed in alphabetical order.
- No – As yet, all long-term studies on the compounds depicted no carcinogenic activity in model organisms. These drugs were not included in final table.
- Unclear – none of the articles in search results described any link between the drug in question and cancer or anti-cancer activity. Further investigation is required to draw any conclusions. These drugs were not included in final table. This category also includes compounds that, according to their FDA drug report sheets, cause neoplasms only when used in very high concentrations.

Results and Discussion

Ion channel drugs that pose a cancer-inducing risk

Table 1 lists ion channel drugs that have been implicated in causing cancer or increasing cell proliferation. Drugs targeting ligand-gated ion channels and voltage-gated ion channels were especially richly represented. Many kinds of cancer were observed by exposure to the listed drugs, including breast, liver, brain, and ovarian cancer.

Ion channel drugs that have potential as anti-cancer treatments

A wide variety of drugs were found to have an anti-cancer effect (Table 2), including those targeting both ligand-gated and voltage-gated ion channels. Both activators and inhibitors were found on the list. As above, the drugs impacted many different kinds of cancer, their targets not limited to just one kind or one tissue type. Categories of channels targeted by drugs identified in this table included 5HT receptor 3 cation channels, ASIC,

Calcium activated chloride channel (CaCC), Calcium- and sodium-activated potassium channels (KCa, KNa), Calcium activated potassium channel, Calcium channel, Chloride Channels, chloride channels of ionotropic GABA receptors, Cyclic nucleotide-regulated channels, epithelial sodium channels (ENaC), glycine receptor, IP3 Receptor, Nicotinic acetylcholine, Ryanodine receptors (RyR), Transient Receptor Potential channels (TRP), Two-pore domain potassium channels (K2P), Voltage gated sodium channels, Voltage-gated calcium channels (CaV), Voltage-gated potassium channels (Kv), Voltage-gated potassium channels (Kv), Voltage-gated sodium channels (NaV), Volume regulated chloride channels (VRAC).

Beyond simple mappings for drugs

Table 3 outlines drugs that appeared in the initial IUPHAR drug database or DrugBank database as ion channel antagonists or activators; however, ion channels are not their primary target. These were added to a separate table because their anti-cancer or cancerous effect could arise from affecting the cells via a different pharmacokinetic pathway, and this effect may be dominant to the effect brought on by targeting the ion channels.

Interestingly, some drugs were present in both cancer and anti-cancer categories (likely hinting at the fact that other aspects, such as timing of application, were crucial to their effect, beyond just the nature of the drug and dosage). For instance, diltiazem and capsaicin were indicated as cancer and anti-cancer in separate studies. We also noticed categories repeating themselves across the two tables, such as voltage gated sodium channels, voltage gated potassium channels, and the TRP family. For example, the category of drugs affecting “glycine receptors” appeared in both cancer and anti-cancer tables. Glycine receptor drugs such as pregnenolone, and nifedipine were flagged in the cancer category, while glycine receptor drugs like HU-210, ketamine, bilobalide, and tropisetron appeared in the anti-cancer category.

Drugs in common use: categories of special interest

We especially tried to determine whether any drugs from the following groups were cancer-causing or not: Proton Pump Blockers, Calcium Channel Blockers, Antiarrhythmics, Anticonvulsants, Anesthetics (ester- and amide-linked), and Gap Junction Blockers (Wu et al. 2002; Beiderbeck-Noll et al. 2003; Soriano-Hernandez et al. 2012; Matsushita et al. 2013; Su et al. 2013; Ahern et al. 2014; Chen et al. 2014; Chang et al. 2015; Luo et al. 2015; Zibara et al. 2015; Ma et al. 2016; Roohbakhsh et al. 2016; Xuan et al. 2016; Bouriez et al. 2018; Li et al. 2018; Wang et al. 2018a; Abdelaleem et al. 2019; Li et al. 2019b; Kristensen et al. 2020; Xie et al. 2020; Xu et al. 2020b; Xu et al. 2020c; Li et al. 2021a; Zhang et al. 2021; Zheng et al. 2021; Huang et al. 2022; Rotshild et al. 2023). Several proton pump inhibitors were found to be associated with an increased risk of cancer, as discussed in (Ahn et al. 2013; Song et al. 2014; Tran-Duy et al. 2016; Abrahami et al. 2022), while certain proton-pump inhibitors such as pantoprazole, omeprazole, esomeprazole, and rabeprazole have also been tied to “anti-

cancer", agreeing with our observation above that ion channel drugs have different effects on cancer depending on the biological context and other subtle aspects of how they are deployed within the organism (Gu et al. 2014; Xu et al. 2020a; Zheng et al. 2021; Mathews et al. 2022; Rotshild et al. 2023).

Limitations of the study

The list of compounds in this meta-analysis is not exhaustive, as the IUPHAR database is not guaranteed to be a comprehensive list of all known drugs affecting ion channels. Moreover, it is quite likely that many cancer-causing and cancer-suppressing effects of available compounds are not yet known; oftentimes drugs are not tested directly for cancer-causing effects *in vitro* and *in vivo*. In such situations, the evidence lies in observational study results and retrospective cohort studies. Additionally, ion channel-targeting drugs like anesthesia are often applied in small, short-lasting dosages, not continuous exposure to body tissue. As such, future studies in specific assays and at specific doses will be needed to clarify the status of the drugs discussed herein for various patient contexts.

Conclusions: cancer electroceuticals

The data from both *in vitro* and *in vivo* studies on bioelectric controls of cell behavior and multicellular coordination have shown a number of key mechanisms by which ion channel drugs can induce or suppress the cancer phenotype. It is now essential to move this knowledge toward clinical application – a task which has already begun (Fukushiro-Lopes et al. 2018) and will continue via the increased study of known compounds and the discovery of new ones. A critical aspect is that bioelectric signals function differently than familiar targets such as signaling proteins and transcription factors. Channels open and close post-translationally, and it's the multicellular pattern of computations performed by the network, within cancer cells and between cancer cells and their environment, not simply whether a single channels up- or down-regulated, that drives outcome (Osswald et al. 2015; Cervera et al. 2020; Venkataramani et al. 2022; Hausmann et al. 2023) (Levin et al. 2017; Cervera et al. 2018; Levin and Martyniuk 2018; Mathews and Levin 2018). Thus, the field needs to develop approaches that modulate pulsed timing of applications, not just molecular specificity and constant dosage, to truly tame and revert the cancer phenotype. This is likely possible, because it has been shown that the complex endogenous morphogenetic cues operating during regeneration and development can normalize cancer (Rose and Wallingford 1948; Illmensee and Mintz 1976; Kasemeier-Kulesa et al. 2008; Costa et al. 2009; Telerman et al. 2010).

Computational platforms are being developed to assist in the effort of predicting and identifying ion channel control knobs, and thus useful drugs, for purposes in regenerative medicine (Pietak and Levin 2016; Pietak and Levin 2017; Churchill et al. 2018; Riol et al. 2021). These platforms will not only help identify ion channels whose modulation is likely to restore anatomical and histological order (Pai et al. 2018), but will

also help mitigate unwanted side effects such as such as disturbances in cardiac repolarization. While the field of drug discovery faces rich opportunities for novel compounds with additional specificity for sub-types, channel-blocking antibodies, etc., the field already has the benefit of a huge set of existing drugs that likely represent an exciting class of cancer electroceuticals (Pio-Lopez and Levin 2023). Taken together, the consilience of work in the fields of non-neural bioelectricity, ion channel pharmacology, and cancer cell biology is an exciting opportunity that will generate deep advances for basic evolutionary developmental biology and biomedical oncology.

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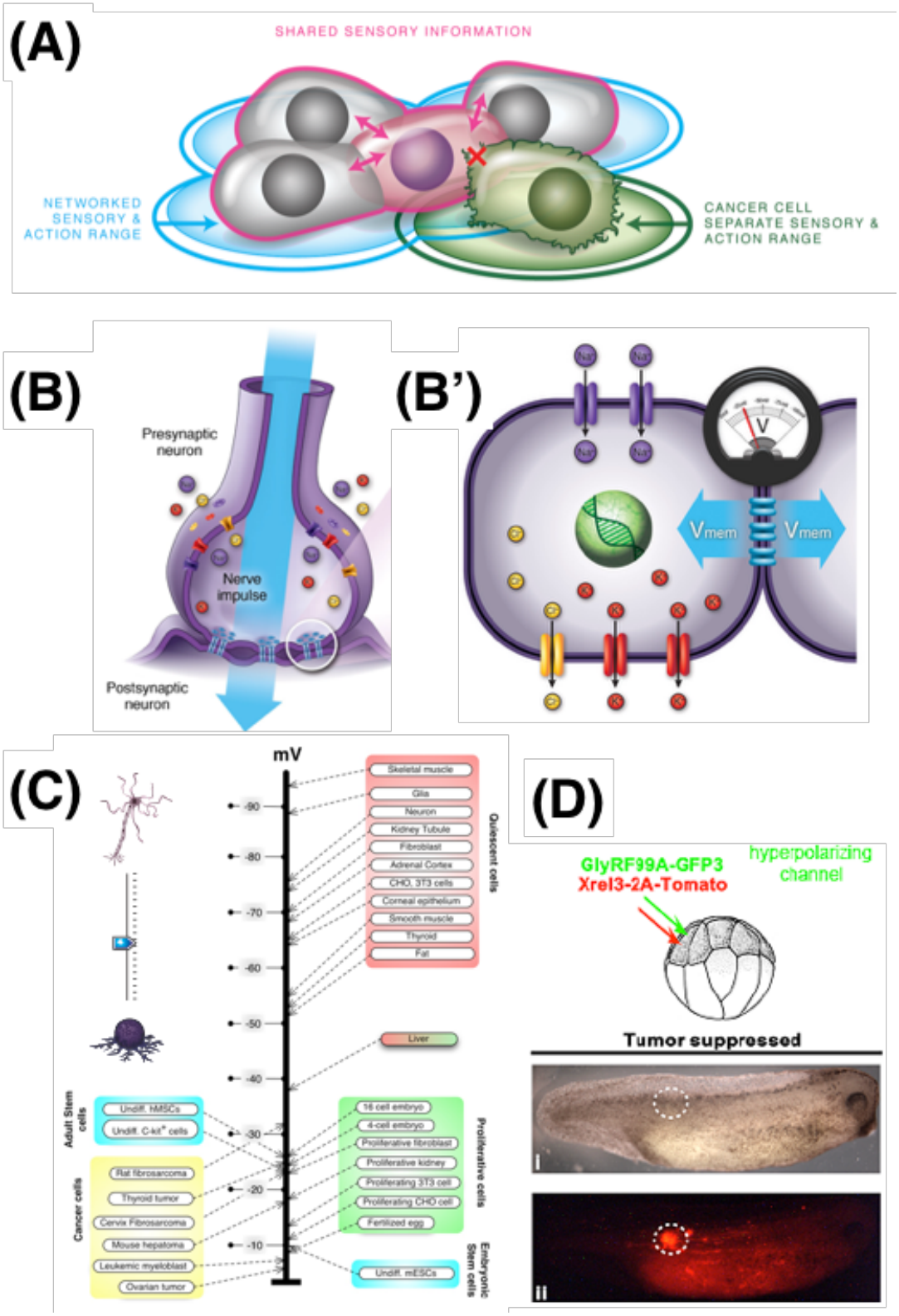
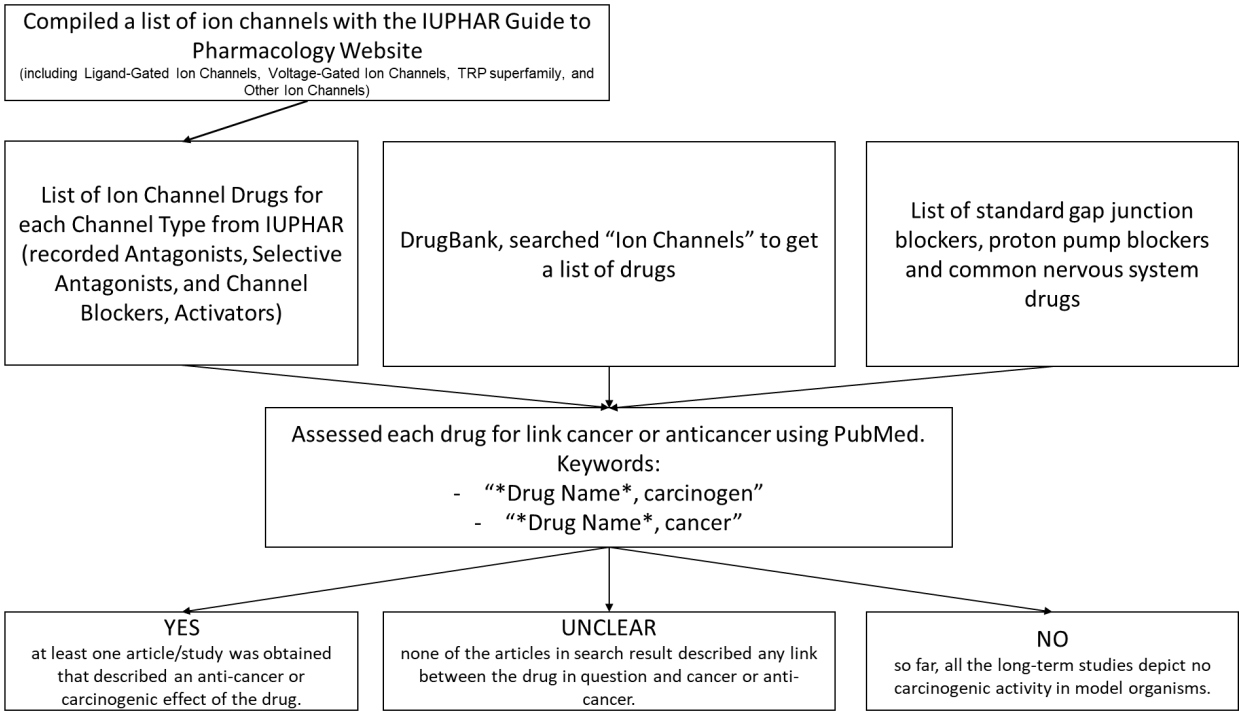
Figure Legends

Figure 1: bioelectric inputs to the cancer phenotype



(A) The ability of cells to cooperate toward large-scale endpoints of tissue and organ homeostasis requires them to communicate as a collective intelligence (Levin 2019; Levin 2021b).
(B) Neurons in the brain communicate and process information via ion channel proteins in their membranes, but all body cells (B') also have ion channels and ways to propagate electrical state information to neighbors in the tissue network.
(C) Individual cell resting potentials readily distinguish between normal adult cells (polarized) and cancer (or embryonic) cells (depolarized).
(D) This relationship is functional (voltage is instructive, not just a marker), as can be seen when a human oncogene (labeled with red fluorescent protein) is injected into a frog embryo, its tumorigenic potential can be abrogated by the co-expression of an ion channel that forces the normal bioelectric state and prevents the cancer phenotype even though the genetic lesion normally causes tumors.

Figure 2: Methods Chart: Flow diagram chart of methodologies and databases used in the search. All "Yes" drugs (n = 109) were included in the tables, segregated by cancer (Table 1), anti-cancer (Table 2), and drugs with off-target ion channel effects (Table 3).



Tables

Table 1: drugs with carcinogenic potential

Ion Channel Target Type	Drug Name	Alternative Targets (if any)	Cancer Type	References
epithelial sodium channels (ENaC)	Triamterene		Hepatocellular adenoma, hepatocellular carcinoma	(National Toxicology 1993b)
$GABA_A$ Receptor	Clonazepam		Thyroid, brain, colorectal	(Iqbal et al. 2015; Kim et al. 2017)
	Lorazepam		Various Cancers, Cancer Biomarkers	(Iqbal et al. 2015; Ku et al. 2018)
	Oxazepam		Hepatocellular adenoma, carcinoma, follicular cell adenoma and hyperplasia,	(National Toxicology 1993a; Kim et al. 2017)
	Phenobarbital	Chloride Channels, Gap junction communication	Hepatocellular carcinoma (liver) Lung cancer Thyroid neoplasms	(Singh et al. 2005; Ohara et al. 2017; Pathak et al. 2020)
	Zolpidem		Brain Cancer	(Hwang et al. 2022)
glycine receptor	Nifedipine	Connexins	Breast Cancer	(Guo et al. 2014)
	Pregnenolone	TRP Channels	Promotes prostate cancer growth	(Roy et al. 2021)
IP3 Receptor	PIP2		Melanoma, Breast Cancer, Leukemia, Prostate Cancer	(Mandal 2020)

Nicotinic acetylcholine	α-conotoxin	Voltage-Gated Sodium Channels	Promotes proliferation of C6 Glioma Cells	(Terpinskaya et al. 2021)
Transient Receptor Potential channels (TRP)	Formalin (formaldehyde)		lung cancer, nasopharyngeal cancer, leukemia non-Hodgkin's lymphoma	(Protano et al. 2021)
Voltage Gate Sodium Channels	Phenytoin		Lyphoma, myeolama, neuroblastoma, Liver tumors	(National Toxicology 1993c; Singh et al. 2005)
Voltage-gated calcium channels (CaV)	Gabapentin	K_v channels	Pancreatic acinar cancer	(Dethloff et al. 2000)
	Diltiazem	5-HT3 and Cyclic nucleotide-regulated channels (CNG)	colon, prostate, skin, lung and a combi-nation of the bladder, ureter and kidney	(Beiderbeck-Noll et al. 2003)
	Praziquantel	schistosome calcium ion (Ca2+) channels	Liver	(Omar et al. 2005)
	Verapamil	blocks TPC channels	colon, prostate, skin, lung and a combi-nation of the bladder, ureter and kidney	(Beiderbeck-Noll et al. 2003)
Voltage-gated potassium channels (Kv)	Capscaicin	TRP and Kv channels, also Chloride channels	Skin carcinogenesis	(Hwang et al. 2010; Bode and Dong 2011; Bley et al. 2012; Lin et al. 2013a)

Table 2: drugs with anti-cancer activity

Ion Channel Target Type	Drug Name	Alternative Targets (if any)	References
5HT3	Tropisetron	Glycine receptor	(Amini-Khoei et al. 2016; Rashidi et al. 2020)
ASIC	Diclofenac	COX-1 and COX-2 inhibitor, sodium channels, potassium channels	(Pantziarka et al. 2016)
	Nafamostat	Mainly affects Serine Protease	(Morimoto et al. 2022)
	Flurbiprofen	Non-steroidal anti-inflammatory agent	(McCormick and Moon 1983)
Calcium activated chloride channel (CaCC)	5-nitro-2-(3-phenylpropylamino)-benzoate (NPPB)		(Yu et al. 2009; Park et al. 2016)
	Tannic Acid	Herg, Potassium, TRP, and Na channels (Zhang et al. 2015)	(Sp et al. 2020; Barboura et al. 2022)
Calcium- and sodium-activated potassium channels	Glibenclamide	Chloride Channels	(Gao et al. 2017)
Calcium activated potassium channel	Senicapoc		Bulk et al. (2015)
Calcium channel	Bepridil	Na(+)-Ca2+ exchange blocker, also ASICs, TPR	(Lee et al. 1995)
	Mibefradil	Calcium- and sodium-activated potassium channels (K_{Ca}, K_{Na}), Volume regulated chloride channels (VRAC), Voltage-gated calcium channels (CaV), Calcium activated chloride channel (CaCC)	(Souza Bomfim et al. 2021)
Chloride Channels	Apigenin	TRPV channels	(Yan et al. 2017)

	Fenofibric acid		(Lian et al. 2018)
	Genistein		(Spagnuolo et al. 2015)
	GlyH-101	Blocks CFTR	(Zhu et al. 2018; Li et al. 2019a)
	ivacaftor		(Liu et al. 2021b)
	Niflumic Acid	Calcium Activated chloride channel (CaCC), Transient Receptor Potential channels (TRP)	(Luo et al. 2015)
	Phloretin		(Choi 2019)
chloride channels of ionotropic GABA receptors	Bilobalide	Also affects glycine receptor	(National Toxicology 2013; Mohanta et al. 2014; Liu et al. 2021a; Tao et al. 2023)
Cyclic nucleotide-regulated channels	Dequalinium		(Pan et al. 2021)
epithelial sodium channels (ENaC)	Benzamil	Na(+)-Ca2+ exchange blocker, TPR	(Lee et al. 1995)
glycine receptor	HU-210	NMDA receptor antagonist	(Casanova et al. 2003)
	Ketamine		(Li et al. 2020; He et al. 2021; Li et al. 2021b)
IP3 Receptor	Decanavate		(Sanchez-Lara et al. 2018; Bijelic et al. 2019)
	Xestospongin		(Cui et al. 2017)

Nicotinic acetylcholine	α-cobratoxin		(Paleari et al. 2009; Arcangeli and Becchetti 2010)
Ryanodine receptors (RyR)	Dantrolene		(Zakaria et al. 2021)
	Ruthenium red	Transient Receptor Potential channels (TRP)	(Anghileri 1975)
	Suramin	inhibit the binding of growth factors (EGF, PDGF, TGF-beta)	(Stein et al. 1989; Bhargava et al. 2007; Li et al. 2015)
Transient Receptor Potential channels (TRP)	Acrolein		(Tsou et al. 2019; Tsai et al. 2021; Tsou et al. 2021)
	Allicin		(Pathak et al. 2020; Catanzaro et al. 2022; Zhou et al. 2022)
	7beta-22 dihydroxyhopane (AP 18)		(Kim et al. 2022)
	Camphor		(Singh et al. 2022)
	Capsazepine		(De La Chapa et al. 2019; Sun et al. 2022)
	Carvacrol		(Li et al. 2021c; Sampaio et al. 2021)
	Cinnamaldehyde		(Lin et al. 2013b; Liu et al. 2020; Aggarwal et al. 2022; Chu et al. 2022)
	Clomitrazole		(Kadavakollu et al. 2014)
	Delta9-Tetrahydrocannabinol		(Milian et al. 2022; Tomko et al. 2022)

	Econazole	Ca^{2+} channel antagonist, anti-fungal	(Choi et al. 2020)
	Englerin A		(Cheung et al. 2018; Grant et al. 2019; Wu et al. 2020; Neo et al. 2022)
	Galangin		(Xiong et al. 2020; Zou et al. 2020; Atwa et al. 2021; Liang et al. 2021b; Long et al. 2022)
	Hyperforin	Reuptake inhibitor of Monoamines	(Chiang et al. 2017; Chen et al. 2018)
	Icilin		(Kim et al. 2011; Valero et al. 2011; Lee et al. 2013; Jahanfar et al. 2022)
	Liquiritigenin	estrogen receptor beta agonist	(Ji et al. 2021; Liang et al. 2021a; Zhang et al. 2022)
	Menthol		(Wang et al. 2012b; Singh et al. 2022)
	Miconazole	Anti-fungal	(Jung et al. 2021)
	Piperine		(Manayi et al. 2018)
	Polygodial		(Fratoni et al. 2018; Garcia et al. 2018; Maslivetc et al. 2021; Venkatesan et al. 2022)
	Thymol		(Islam et al. 2019; Elbe et al.

			2020; Sampaio et al. 2021; Qoorchi Moheb Seraj et al. 2022)
	Tonantzitlolone		(Sourbier et al. 2015; Busch et al. 2016; Rubaiy et al. 2018; de Abrantes et al. 2022)
Two-pore domain potassium channels (K2P)	Anandamide		(Ma et al. 2016)
	R-(+)-methanandamide		(Eichele et al. 2006; Eichele et al. 2009; Olea-Herrero et al. 2009a; Olea-Herrero et al. 2009b; Ortega et al. 2016)
	Riluzole	Transient Receptor Potential channels (TRP)	(Blyufer et al. 2021)
Voltage gated sodium channels	Procaine	Ryanodine receptors (RyR)	(Villar-Garea et al. 2003)
Voltage-gated calcium channels (CaV)	Amlodipine		(Goldstein 2001)
	Diltiazem	5-HT3 and Cyclic nucleotide-regulated channels (CNG)	(El-Mahdy et al. 2020; Chen et al. 2022)
	Pimozide	HERG and KIR channels	(Dakir el et al. 2018; Goncalves et al. 2019; Ranjan et al. 2020)
	TTA-A2		(Kumari et al. 2020)
Voltage-gated potassium channels (Kv)	Atemizole	Antihistamine	(Garcia-Quiroz and Camacho 2011; Chavez-Lopez et al. 2017;

			Hasanovic et al. 2020)
	Capscaicin	TRP and Kv channels, also Chloride channels	(Hwang et al. 2010; Bode and Dong 2011; Bley et al. 2012; Lin et al. 2013a)
	Chlorpromazine	Blockade of histamine H1, dopamine D2, and muscarinic M1 receptors and HERG channels	(Kamgar-Dayhoff and Brelidze 2021; Matteoni et al. 2021; Xu et al. 2022)
	Dendrotoxin		(Jang et al. 2011b)
	Margatoxin		(Jang et al. 2011a; Diaz-Garcia and Varela 2020)
	NS1643		(Breuer et al. 2019; Mathews et al. 2022)
	Terfenadine		(Jangi et al. 2008; Wang et al. 2014; An et al. 2017)
	Tetraethylammonium	Nicotinic acetylcholine receptors and Calcium gated Potassium channels	(Schickling et al. 2011)
Voltage-gated potassium channels (Kv)	Retigabine		(Mathews et al. 2022)
Voltage-gated sodium channels (NaV)	Amiloride	potassium-sparing diuretic, Transient Receptor Potential channels (TRP)	(Sparks et al. 1983; Matthews et al. 2011)
	Desipramine	Inwardly rectifying potassium channels (KIR)	(Yang and Kim 2017)
	Ethyl-isopropyl amiloride (EIPA)	inhibitor of Na(+)/H(+) exchanger Also ASICs	(Hosogi et al. 2012)

	Veratridine		(Abdullah et al. 2015; Freeling et al. 2022)
Volume regulated chloride channels (VRAC)	Gossypol		(Cao et al. 2021; Cai et al. 2022; Lee et al. 2022; Renner et al. 2022)
	Nordihydroguaiaretic acid		(Gao et al. 2011; Hernandez-Damian et al. 2014; Hsu et al. 2014; Mundhe et al. 2015; Kimura and Huang 2016; Terpinskaya et al. 2021)
	NS3728		(Sauter et al. 2015)

Table 3: Drugs with off-target effect on ion channel

Ion Channel Target Type	Drug Name	Cancer effect	References
Dopamine Receptor and Several Ion Channels	Trifluoperazine	Anti-Cancer	(Yeh et al. 2012; Xia et al. 2019)
ASIC, COX inhibitor	Aspirin (includes Salicylic acid)	Anti-Cancer	(Cao et al. 2016; Nounu et al. 2021; Imai et al. 2022; Ma et al. 2022)
ASIC, Voltage-gated proton channel (Hv1)	Cadmium^{2+}	Cancer	(Hague et al. 2000; Hong et al. 2006; Wang et al. 2012a; Genchi et al. 2020)

Transient Receptor Potential channels (TRP)	URB597	Anti-Cancer	(Hamtiaux et al. 2012)
SSRI Inhibitor	Fluoxetine	Anti-Cancer	(Tuszynski et al. 2017; Yang et al. 2021)
Transient Receptor Potential channels (TRP)	Lanthanum^{3+}	Anti-Cancer	(Kapoor 2009) (Wang et al. 2018b) (Lu et al. 2020)
Voltage-gated calcium channels (CaV)	Nickel $^{2+}$	Carcinogen	(Grimsrud and Andersen 2012)
Voltage-gated sodium channels (NaV)	Tamoxifen	Cancer	(Stearns and Gelmann 1998; Brown 2009; Yasue et al. 2011)
Volume regulated chloride channels (VRAC)	Clomiphene	Cancer	(Unkila-Kallio et al. 2000; Althuis et al. 2005; Reigstad et al. 2017; Yilmaz et al. 2018)
Volume regulated chloride channels (VRAC)	Nafoxidene	Anti-Cancer	(Bloom and Boesen 1974; Legha et al. 1976; Moseson et al. 1978; Steinbaum et al. 1978)

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