**Review**

**T-Type Calcium Channels: A Mixed Blessing**

Dario Melgari 1, Anthony Frosio 1, Serena Calamaio 1, Gaia A. Marzi 2, Carlo Pappone 1,3,4 and Ilaria Rivolta 1,2,*

1 Institute of Molecular and Translational Cardiology, IRCCS Policlinico San Donato, Piazza Malan 2, 20097 San Donato Milanese, Italy 
2 School of Medicine and Surgery, University of Milano-Bicocca, Via Cadore, 48, 20900 Monza, Italy 
3 Arrhythmology Department, IRCCS Policlinico San Donato, Piazza Malan 2, 20097 San Donato Milanese, Italy 
4 Faculty of Medicine and Surgery, University Vita-Salute San Raffaele, Via Olgettina 58, 20097 Milan, Italy

* Correspondence: ilaria.rivolta@unimib.it

**Abstract:** The role of T-type calcium channels is well established in excitable cells, where they preside over action potential generation, automaticity, and firing. They also contribute to intracellular calcium signaling, cell cycle progression, and cell fate; and, in this sense, they emerge as key regulators also in non-excitable cells. In particular, their expression may be considered a prognostic factor in cancer. Almost all cancer cells express T-type calcium channels to the point that it has been considered a pharmacological target; but, as the drugs used to reduce their expression are not completely selective, several complications develop, especially within the heart. T-type calcium channels are also involved in a specific side effect of several anticancer agents, that act on microtubule transport, increase the expression of the channel, and, thus, the excitability of sensory neurons, and make the patient more sensitive to pain. This review puts into context the relevance of T-type calcium channels in cancer and in chemotherapy side effects, considering also the cardiotoxicity induced by new classes of antineoplastic molecules.

**Keywords:** T-type Ca\textsuperscript{2+} channel; T-type calcium channel blocker; cancer therapy; cardiotoxicity; peripheral neuropathy; mibefradil; bortezomib; carfilzomib

1. T-Type Calcium Channels

Transient T-type or Low-Voltage Activated (LVA) calcium (Ca\textsuperscript{2+}) channels are voltage-dependent ion channels that open at relatively low membrane potentials (i.e., between −70 to −60 mV, with maximum peak current between −30 to −10 mV), allowing extracellular calcium to enter the cell, and which rapidly inactivate (i.e., tau of 15–30 ms) and slowly deactivate [1,2]. The low threshold of activation, not far from the resting potential of most excitable cells, together with their fast kinetics, makes T-type Ca\textsuperscript{2+} channels key modulators of cellular excitability and pacemaking [2,3]. Moreover, T-type Ca\textsuperscript{2+} channels have a voltage range of activation that overlaps that of their steady-state inactivation, meaning that, over a small near-resting voltage range, a fraction of channels can open without completely inactivating, generating a “window” current, distributed around −60/−50 mV, that modulates intracellular calcium levels [4]. T-type Ca\textsuperscript{2+} channels are involved in multiple physiological processes, such as neuronal firing, nociception, electrical automaticity, blood vessel constriction and dilation, lymphatic vessel pacemaking and contraction, smooth muscle contraction, myoblasts fusion, neurotransmitter release, fertilization, cell growth, differentiation, and proliferation [2,5–7]. Thus, they are expressed in a variety of excitable and non-excitable tissues in which they display distinctive behaviors at the pharmacological and kinetic (especially in terms of inactivation) levels. This is partly due to the differential and heterogeneous expression of the following three independent T-type channel genes that encode, respectively, for the three alpha subunit subtypes named Cav3.1, Cav3.2, and Cav3.3: CACNA1G, CACNA1H, and CACNA1I [8–10]. Similar to other Ca\textsuperscript{2+} channels,
like the long-lasting L-type High-Voltage Activated (HVA) ones (i.e., Cav1.x and Cav2.x), the Cav3.x alpha pore-forming subunit is organized into four domains (DI–DIV), each formed by six transmembrane segments (S1–S6), where the S4 segment contains multiple positively charged arginine or lysine residues that serve as a voltage sensor, and with the pore comprised of between segments S5 and S6. This region, responsible for selective permeability, contains four key acidic glutamate or aspartate residues [11]. In particular, the selectivity filter is determined by two glutamate residues in domains I and II and two aspartate residues in domains III and IV, a structure that differs from the one composed of four glutamate residues found in HVA Ca\(^{2+}\) channels [12]. In contrast to Cav1.x and Cav2.x, Cav3.x alpha channels do not have either the alpha-interaction domain (AID), an 18-residue sequence in the I-II intracellular linker loop necessary for the interaction with the beta subunit and conserved among all HVA Ca\(^{2+}\) channels, nor the IQ calmodulin-binding motif (“IQ” derives from the first two conserved residues of the motif itself) located in the cytoplasmic C-terminal tail and which binds calmodulin. Moreover, LVA Ca\(^{2+}\) channels do not seem to co-assemble with ancillary subunits, and expression of just the Cav3.x alpha is enough to recapitulate the native T-type current waveforms [9]. Within the family of T-type Ca\(^{2+}\) channels, Cav3.1 and Cav3.2 can be distinguished from each other through their different sensitivities to nickel inhibition and by their kinetics of recovery from inactivation, while Cav3.3 is characterized by much slower kinetics of activation and inactivation [13,14]. Another level of complexity is given by multiple alternative splicing variants that differ at both pharmacological and electrophysiological levels [15]. Despite functional and pharmacological differences, subtype-specific experimental tools (e.g., inhibitors) are still lacking (the ones available are summarized in Table 1), making the study of T-type Ca\(^{2+}\) channels in native tissues and cells particularly intricate [3,15], but still necessary for a complete understanding of their physiological and pathophysiological role.

### Table 1. T-type Ca\(^{2+}\) channel blockers.

| Drug                | Chemical Class/Origin | Preferential Block | Treatment Indication                                      | References |
|---------------------|-----------------------|--------------------|-----------------------------------------------------------|------------|
| (3R,5S)-31c         | Benzodiazepine        | Cav3.3 > Cav3.1 > Cav3.3 | Absence epilepsy                                          | [16]       |
| A1048400            | Diphenylpiperazine    | T-type and N-type  | Tactile allodynia in capsaicin-induced secondary hypersensitivity (animal model) | [17,18]   |
| A-686085            | Diphenylpiperazine    | L-, N- and T-type  | Tactile allodynia in capsaicin-induced secondary hypersensitivity (animal model) | [18]       |
| ABT-639             | Sulfonamide           | Cav3.2             | Diabetic Neuropathy, failed clinical trials for pain/schizophrenia treatment | [19]       |
| ACT-709478          | Heteroaaromatic amide | Cav3.1 > Cav3.3 > Cav3.2 | Generalized epilepsy (Phase II)                           | [20]       |
| Amiodarone          | Na, K and Ca          |                    | Class III Antiarrhythmic agent                          | [21]       |
| Amlodipine (Norvasc)| DHP                   | Cav3.2 > Cav3.1 and Cav3.3 | High blood pressure and coronary artery disease | [17]       |
| Anandamide          | Endocannabinoids      | T-type             |                                                           | [16]       |
| Arachidonyl-glycine | Anandamide derivative | T-type             |                                                           | [16]       |
| Aranidipine (Sapresta) | DHP                | L- and T-type     | High blood pressure                                    | [17]       |
| Azelnidipine (CalBlock) | DHP              | L- and T-type     | High blood pressure                                    | [17]       |
| Barbindipine        | DHP                   | L- and T-type     | Hypertension                                             | [17]       |
| Bay K8644           | DHP                   | L- and T-type     |                                                           | [21]       |
| Benidipine (Coniel) | DHP                   | L- and T-type     | Hypertension                                             | [17]       |
| Bepridil            | Diamine               | Non selective     | Angina                                                   | [21]       |
### Table 1. Cont.

| Drug                | Chemical Class/Origin | Preferential Block | Treatment Indication                                      | References |
|---------------------|-----------------------|--------------------|-----------------------------------------------------------|------------|
| Compound 10d        | Hexane derivatives    | T-type, hERG, N-type | Neuropathic pain (animal model)                            | [16]       |
| Compound 10e        | Piperazine derivative | Cav3.1, Cav3.2, Cav3.3, No strong effect on Cav1.2 and Cav2.2 | CFA-induced inflammatory pain.                           | [16]       |
| Compound 9b         | Sulfonamides          | T-type, N-type > hERG | Cold allodynia, mechanical pain hypersensitivity (animal model) | [16]       |
| Compound 9c         | DHP derivative        | Cav3.2 > Cav1.2     | Inflammatory pain (animal model)                          | [16]       |
| Compound series     | Hybrids of NMP-7 and TTA-A1 | Potent Cav3.2 inhibition | Cav3.2-related neuropathic and inflammatory pain (animal model) | [16]       |
| D888 (devapamil)    | Phenylalkylamine derivative | L- and T-type (Cav3.2) | Stress induced ulcer in rats                              | [21]       |
| Diltiazem           | DHP                   | Non selective       | High blood pressure, angina, arrhythmias                  | [21]       |
| Efondipine (Landel) | DHP                   | L- and T-type       | Hypertension                                               | [17]       |
| Ethosuximide (Zarontin) | Succimide             | Cav3.1              | absence epilepsy                                           | [20]       |
| Felodipine          | DHP                   | L- and T-type       |                                                           | [21]       |
| Flunarizine         | Diphenylpiperazine derivative | T-type | Neuroepileptic agent                                      | [22]       |
| Fludoxetine (Prozac)| Selective serotonin reuptake inhibitors (SSRI) | Cav3.1, Cav3.2, Cav3.3 | Depression                                                | [23]       |
| Haloperidol         | Butyrophenone         | T-type              | Neuroepileptic agent                                       | [22]       |
| Isradipine          | DHP                   | Cav3.2              |                                                           | [21]       |
| Kurtxin             | Scorpion venom        | L- and T-type       |                                                           | [24]       |
| KYS05041            | 3,4-Dihydroquinazoline derivative | T-type | In vitro inhibition of cancer cells growth                 | [25,26]    |
| KYS05047            | 3,4-Dihydroquinazoline derivative | Cav3.1, Cav3.2 | Effective on neuronal circuits                            | [17]       |
| KYS-05090S          | 3,4-dihydroquinazoline derivative | Cav3.1, Cav3.2 | Inflammatory and neuropathic pain                         | [16]       |
| Mibebradil (Posicor)| Phenylalkylamine      | L- and T-type, Na and K | Hypertension and angina (withdrawn)                        | [17,27]    |
| MK-8998 (Suvecallamide) | Pyridyl amide | T-type | Failed clinical trials for pain/schizophrenia treatment | [19]       |
| ML218               | DHP                   | Cav3.1, Cav3.3      |                                                           | [17]       |
| N10 and N12         | DHP derivative        | T-type              | Inflammatory pain (animal model)                          | [16]       |
| NCC 55-0396         | T-type                | Tumor-induced angiogenesis in vitro and in vivo              | [17]       |
| Nicardipine (Cardene)| DHP                  | L- and T-type       | Hypertension and angina                                    | [17]       |
| Niguldipine         | DHP                   | L- and T-type       |                                                           | [21]       |
| Nimodipine (Nimotop) | DHP                  | L- and T-type       | Cerebral vasospasm, ischemia                               | [17]       |
| Nisoldipine         | DHP                   | L- and T-type       |                                                           | [21]       |
| NMP-181             | NMP-7 derivative      | CB2 agonist, T-type blocker       | Formalin-induced inflammatory pain (animal model)            | [16]       |
| NMP-7               | Carbazole derivative  | Cannabinoid receptors CB1 and CB2 agonist, T-Type blocker | Formalin-induced inflammatory pain (animal model)             | [16]       |
Table 1. Cont.

| Drug          | Chemical Class/Origin | Preferential Block                                                                 | Treatment Indication                  | References |
|---------------|-----------------------|------------------------------------------------------------------------------------|---------------------------------------|------------|
| Penfluridol   | Diphenylbutylpiperidines | D2 dopamine receptor antagonist, T-type and L-type blocker                        | Neuroepileptic agent                  | [22,25]    |
| Perhexiline   |                       | L- and T-type (Cav3.2)                                                           | Coronary vasodilator, angina          | [21]       |
| Pimozide      | Diphenylbutylpiperidines | D2 dopamine receptor antagonist, T-type and L-type blocker                        | Neuroepileptic agent                  | [22,25]    |
| ProTx I       | Tarantula venom       | Cav3.1 (Blocks also NaV)                                                         | Increased bladder capacity in bladder outlet obstruction model | [28]       |
| ProTx II      | Tarantula venom       | Cav3.2 (Blocks also NaV)                                                         |                                      | [28]       |
| RQ-00311610   |                       | T-type                                                                            | Human cancer prostate cell proliferation |            |
| TH-1177       | Chemical synthetic peptide |                                                                               |                                      | [25]       |
| Trazodone     | Serotonin antagonist and reuptake inhibitors (SARIs) | Cav3.1, Cav3.3                                                                    | Depression                            | [29]       |
| TTA-A2        |                       | Cav3.1, Cav3.3                                                                     | Effective on neuronal circuits         | [17]       |
| TTA-P2        | 4-aminomethyl-4-fluoropiperidine derivative | T-type                                                                            | Antinociceptive agent                 | [17]       |
| Verapamil     | Phenylalkylamine       | L- and T-type                                                                      | High blood pressure and angina, supraventricular tachycardia | [30]       |
| VH04          |                       | Cav3.1                                                                            |                                      | [17]       |
| Z941/944      |                       | T-type                                                                            |                                      | [17]       |
| Z944          | Piperazine             | T-type                                                                            | Pain (Phase II)pain                   | [20]       |
| Zonizamide (Excegran) | Sulfonamide         | Cav3.2 (non selective)                                                            | Epilepsy                              | [17,20]    |

2. T-Type Ca\(^{2+}\) Channels in the Heart

In the heart, T-type Ca\(^{2+}\) channels had been traditionally considered a minor player in cardiac calcium handling. In fact, the vast majority of calcium influx responsible for cardiomyocytes contraction is managed by the more abundantly expressed HVA Ca\(^{2+}\) channels. This view has developed over the last 30 years, and, nowadays, cardiac T-type Ca\(^{2+}\) channels are considered key regulators of cardiac automaticity, development, and excitation-contraction coupling in several animal models, including mouse, rat, cat, pig, and dog [2,31]. At the cardiac level, T-type Ca\(^{2+}\) current (IC\(_{\text{CaT}}\)) is carried mainly by the Cav3.1 and Cav3.2 sub-types [31,32]. Their expression in cardiac tissue reaches a maximum in embryonic development and dramatically falls in the post-neonatal phase [31,32]. In particular, the amount of T-type Ca\(^{2+}\) channels decrease by about 80% from the embryonic stage to adulthood [33]. During fetal development, Cav3.2 is the most abundant sub-type expressed throughout the heart [34]. In the perinatal stage, the expression of Cav3.2 starts to decrease, while Cav3.1 levels rise and become the predominant adult cardiac sub-type [35]. In the adult heart, T-type Ca\(^{2+}\) channels are not expressed in ventricular myocytes, and tend to localize in the conduction system, and in all cell types, characterized by automaticity; where they exert a pacemaker role and function in the depolarization of the sinoatrial nodal cells. The Cav3.1/Cav3.2 ratio varies between different animal models, probably underlying the distinctive heart rates of different mammalian species [31]. Moreover, an inverse correlation has been described between sinoatrial IC\(_{\text{CaT}}\) amplitude and body size, with smaller animals exhibiting a more prominent T-type current [1]. Despite this body of evidence, IC\(_{\text{CaT}}\) has never been directly recorded in human nodal cells [1,36]. On the other hand, transcripts of both Cav3.1 and Cav3.2 have been found in the human sinoatrial node [8,37], with only Cav3.1 detected at the protein level [38]. Some evidence suggests a functional role of IC\(_{\text{CaT}}\) in humans, as oral administration of mibefradil, a relatively selective T-type Ca\(^{2+}\)
channel inhibitor, reduced the pacemaker activity of the sinus node [39]. Finally, T-type Ca\(^{2+}\) channels are involved in the diseased heart. Indeed, despite not being expressed in healthy adult cardiomyocytes, as already mentioned, an increase in ICa\(_T\) has been reported in several animal models of heart failure and cardiac hypertrophy [32,40,41]. A greater expression of ICa\(_T\) can lead to alteration of intracellular calcium handling, intracellular calcium accumulation, and unbalanced calcium signaling. In fact, as demonstrated by knock-out mice, Cav3.2 is involved in the cardiac hypertrophic response, either mediated by mechanical stress, pressure overload, or angiotensin II infusion [42].

3. T-Type Ca\(^{2+}\) Channels in Pain Modulation and in Chemotherapy-Induced Peripheral Neuropathy

T-type Ca\(^{2+}\) channels were first described in peripheral sensory neurons whose cell bodies are located in the dorsal root ganglia (DRGs) [43]. DRGs are key sites for the mechanism underlying chronic and/or neuropathic pain perception [44]. Within this context, T-type Ca\(^{2+}\) channels, and in particular the Cav3.2 sub-type, are key players in the acute nociceptive processing induced by reducing agents [45] and are also associated with chronic pain symptoms in rats with peripheral axonal injury [46]. Interestingly, Cav3.2 seems to be particularly highly expressed in a subpopulation of nociceptive, capsaicin-sensitive DRG neurons (called “T-rich”) which exhibit T-type, but not L-type, calcium currents [47]. The role of Cav3.2 in pain perception is confirmed by several studies on different pain models in which channel expression and/or activity are increased after pain-inducing treatments, such as DRG chronic compression, spinal nerve ligation, paclitaxel-induced peripheral neuropathy, and others (for review see [48]). Despite the mounting evidence of an association, the mechanism underlying the increase of Cav3.2 in pain models remains elusive. There is a general inconsistency among studies focused on changes in total protein expression, as some reported an increase while others have observed no change. More agreement is found regarding surface protein expression which is suggested to be augmented in both early and late phases of chronic pain [49,50]. At least, in the latter, this is thought to be related to reduced internalization, due to lower levels of ubiquitination as a direct consequence of the overexpression of the ubiquitin-specific cysteine protease 5/isopeptidase (USP5) [51,52], which interacts with the III-IV linker of the Cav3.2 T-type channel, enhancing its stability.

T-type Ca\(^{2+}\) channels are also involved in a specific form of peripheral neuropathy induced by chemotherapy (CIPN). CIPN is a major dose-limiting side effect of several anticancer agents, such as immunomodulatory, platinum-based drugs, vinca alkaloids, epothilones, taxanes, and proteasome inhibitors [53,54]. Immunomodulatory drugs (e.g., thalidomide) are used in the treatment of multiple myeloma. They induce CIPN by down-regulating TNF-\(\alpha\) and accelerate neuronal cell death. Platinum-based (e.g., oxaliplatin, cisplatin and carboplatin) antineoplastic drugs are widely used in the treatment of several types of solid tumors. Their involvement in CIPN is due to their effect, among others, on the activity of potassium channels, transient receptor potential (TRP) and voltage-gated sodium channels (Nav 1.6, 1.7 and 1.9). Indeed, an increase in Na\(^{+}\) conductance and a reduction in the threshold potential and membrane resistance result in hyperexcitability of peripheral neurons [54]. Vinca alkaloids, used in breast cancer, germ cell tumors, Hodgkin and non-Hodgkin lymphomas, osteosarcoma, and neuroblastoma, inhibit the assembly of microtubules and promote their disassembly, thus disrupting axonal transport and leading to metaphase arrest. They are known to alter the expression of ion channels [54]. Epothilones (e.g., ixabepilone), used in the treatment of breast, ovarian, prostate, and non-small cell lung cancer act as tubulin destabilizers, causing impairment of cancer cell division leading to cell death. Meanwhile, they are responsible for the impairment of axonal transport of synaptic vesicles loaded with essential cellular components, including ion channels. Taxanes (e.g., paclitaxel, docetaxel, and cabazitaxel), are used for the treatment of ovarian, breast, non-small cell lung cancer and prostate cancer [55]. Similar to epothilones, they bind to the \(\beta\)-tubulin subunit, stabilizing the microtubule structure and preventing
depolymerization. This condition leads to the arrest of the cell cycle at the G2/M phase. Moreover, microtubule stabilization modifies the expression and function of Na\(^+\), K\(^+\), and TRP ion channels. In particular, they decrease the expression of potassium channels and increase that of sodium Nav1.7 channels, which results in the hyperexcitability of peripheral neurons.

Additionally, taxanes exert a direct effect on Cav3.2 and IC\(_{\alpha T}\). In fact, Taxol (paclitaxel), the most commonly used taxane, has a >50% probability of inducing peripheral neuropathy, which can become chronic and irreversible in a subgroup of patients [56]. Moreover, Li and colleagues showed that, in neurons isolated from rat DRGs, Taxol increased both Cav3.2 expression and IC\(_{\alpha T}\) density [57]. The treatment also left-shifted both the IC\(_{\alpha T}\) voltage-dependent activation and the steady-state inactivation curves, increasing the number of available channels and potentially lowering the neuronal firing threshold [57].

Another chemotherapeutic agent that causes CIPN through a direct effect on Cav3.2 is the boronic acid dipeptidase 20S proteasome complex inhibitor bortezomib (BTZ). This class of antineoplastic drug has been developed to tackle cancer, since an over-activation of the proteostatic system machinery (e.g., the ubiquitin proteasome- and the autophagy lysosome-degradation systems) is a well-known characteristic of advanced tumors [58–60]. By inhibiting proteasome degradation, BTZ elevates Cav3.2 protein levels and the related current in afferent neurons, leading to BTZ-induced peripheral neuropathy (BIPN). BTZ is commonly used in the treatment of multiple myeloma and mantle cell non-Hodgkin’s lymphoma [61] and exerts its therapeutic action by inducing an arrest of the cell cycle, upregulating pro-apoptotic genes, and downregulating key factors of angiogenesis, stroma adhesion, cell proliferation and survival [62,63].

Despite BTZ efficacy, BIPN is one of the most severe non-hematological side effects of chemotherapeutic agents against multiple myeloma [61]. The ability of BTZ to inhibit proteasome activity in DRG neurons has been demonstrated in rat and mice models of BIPN [64,65]. In a recent study, Tomita and colleagues showed that in a mouse model of BIPN, the protein expression of Cav3.2 and USP5 was upregulated without increasing mRNA levels, suggesting that BTZ increases Cav3.2 protein level by reducing its proteasomal degradation. In fact, BIPN was reversed by knockdown of Cav3.2 and by the administration of T-type channel blockers, including the state-dependent blocker TTA-2, the state-independent blocker PNG, the PNG-analogue KTt-45, and ascorbic acid, which selectively blocks Cav3.2 but not Cav3.1 and Cav3.3 [66]. Interestingly, another new generation proteasome inhibitor, carfilzomib (CFZ), showed minimal neurotoxicity and fewer and milder off-target effects compared to BTZ [67]. This reduced toxicity is thought to be due to higher selectivity of CFZ for the chymotrypsin-like activity of the β5 sub-unit of the 20S core particle of the proteasome [68]. On the other hand, CFZ treatment was associated with a 5% incidence of unpredictable cardiovascular events, including congestive heart failure, pulmonary edema, decreased ejection fraction, cardiac arrest, and myocardial ischemia [69]. BTZ therapy itself, though, is not without cardiac side effects responsible for therapy discontinuation [70,71].

4. The Ubiquitin-Proteasome System and Proteasome Regulation of Cardiac Ion Channels

The Ubiquitin-Proteasome System (UPS) is one of the major protein degradation systems in eukaryotic cells and it accounts for up to 90% of the degradation of long- and short-lived and abnormal intracellular proteins [72]. Despite the cytosolic localization of its components, the UPS can target proteins from the plasma membrane, nucleus, and even from the ER lumen [73]. The pathway through which a protein undergoes UPS degradation is composed of two distinct events: first, a chain of multiple ubiquitin molecules is covalently attached to the target protein, and second, the tagged protein is transported to the proteasome for degradation. The structure and function of the proteasome have been extensively studied and reviewed [74–79] and go beyond the scope of this review. The proteasome and the ubiquitin-activating enzymes are constitutively active. Nevertheless, UPS is finely regulated, as the ubiquitination state of a protein is a dynamic counterbalance
between ubiquitination and de-ubiquitination [73]. This machinery is of course involved in the regulation of the surface expression not only of T-type but also of several ion channels. The incubation with the proteasome inhibitor MG132, a structural and functional analog of BTZ that enhances Cav3.2 activity in rat DRGs [51], extended the half-life of cardiac Kv1.5 expressed in COS cells, inducing a significant increase in the protein expression level and current amplitude [80]. The expression of the hERG potassium channel, the product of the human ether-a-go-go related-gene, at the membrane of HEK cells, is also regulated by the UPS system [81,82], and proteasomal inhibition by BTZ, MG132, and other drugs rescued trafficking-deficient LQT2-related and schizophrenia-related hERG channel variants [83–86]. In addition to calcium and potassium channels, the cardiac Nav1.5 sodium channel is also targeted by the UPS [87]. MG132 increased its protein expression and current density in isolated neonatal rat cardiomyocytes and rescued the Nav1.5 reduction in cardiomyocytes of dystrophin-deficient mdx5cv mice [88,89]. Interestingly, in Schistosoma mansoni parasites, MG132 caused a decreased expression of transcripts of different ion channels, including the HVA Ca\textsuperscript{2+} channels, Ca\textsuperscript{2+}-activated potassium channels, and ATP-sensitive potassium channels, an effect opposite to that observed in different animal models [90]. That said, it is not surprising that inhibition of the proteasome machinery leads to alterations in excitability, with deleterious effects on neuronal and cardiac activity.

5. Paclitaxel, Bortezomib, and Carfilzomib Cardiotoxicity: A New Field That Needs to Be Explored

It is well established that chemotherapeutics induce cardiotoxicity to the point that the field of cardio-oncology has developed. Although the definition of cardiotoxicity commonly indicates a decline in patients’ cardiac function, the spectrum of cardiac side effects of chemotherapeutic treatment is heterogeneous and includes impairment in ventricular depolarization or repolarization and QT interval alterations, arrhythmia, bradycardia, tachycardia, decreases in left ventricular ejection fraction and fractional shortening, and irreversible congestive heart failure [91]. All of which worsen patient quality of life and increase mortality. Anthracyclines are considered the most common culprit drugs causing chemotherapy-induced cardiotoxicity, (acute events in 0.4–41% of patients and chronic events in 0.4–23%) followed by fluoropyrimidines (3–19%) [92,93]. Taxanes are in third position with an epidemiology of 3–20% cardiotoxic events, the most common of which are arrhythmia and cardiac ischemia. In particular, paclitaxel treatment causes acute or sub-acute bradycardia in 30% of patients, cardiac ischemia in 5% of treated patients [91], heart block, and atrial or ventricular arrhythmias in a smaller fraction of patients (0.5%) and restricted left ventricular pump function, and can provoke chronic cardiotoxicity with clinical symptoms of cardiac insufficiency even decades after the end of treatment [94].

BTZ and CFZ cardiotoxicity is still a matter of debate. Clinical data are conflicting, as cardiac events are not clearly related to significant cardiovascular risk factors, such as existing cardiac diseases or co-administration of known cardiotoxic drugs [62,95]. Even if rare, BTZ-associated cardiac events have been reported, and include heart failure (the most common), complete atrioventricular block, atrial fibrillation and other forms of arrhythmias, pericardial effusion, orthostatic hypotension, and ischemic heart disease [62,70,71]. CFZ is considered more cardiotoxic than BTZ and it has also been associated with a higher incidence of cardiac arrhythmias [96]. These uncommon events may suggest a mild effect of BTZ and CFZ on the cardiac tissue, that can become life-threatening in the presence of cardiac risk factors and/or compromised substrates.

Animal models have been used to investigate the mechanism behind BTZ and CFZ alleged cardiotoxicity. In male Wistar rats, the administration of BTZ led to left ventricular contractile dysfunction with impaired cardiomyocyte contractility, due to mitochondrial alteration, and reduced ATP production [97]. Moreover, Hasinoff and colleagues recently tested both BTZ and CFZ on primary neonatal rat cardiomyocytes showing that the two compounds induced cell damage at sub-micromolar concentrations. The study argued that the proteasomal inhibition within a cellular environment, characterized by elevated sarcom-
eric protein turnover, led to cellular damage and subsequent cell death and apoptosis [98]. In another study, Tang and colleagues pointed to an overactivation of the hypertrophy-related calcineurin and nuclear factor of activated T-cells (NFAT) signaling pathway as the culprit for BTZ cardiotoxicity in cultured and in vivo murine cardiomyocytes. In particular, the administration of BTZ induced left ventricular hypertrophy, heart failure, and premature death [99].

Despite the evidence, the mechanisms behind BTZ and CFZ cardiotoxicity remain elusive. As reported above, BTZ has a direct effect on the Cav3.2 level of expression in rat DRGs through inhibition of channel ubiquitination and internalization [66]. In the heart, the UPS is the principal protein degradation system, managing the turnover of up to 90% of the cellular proteins [100], and alteration in the UPS can lead to several cardiac diseases, including cardiac hypertrophy, chronic heart failure, and remodeling [101]. It is, therefore, intriguing that to date no studies have been published regarding the potential cardiomyocyte electrophysiological consequences of inhibition of the cardiac proteasome by BTZ and CFZ and the potential of T-type calcium channels as a pharmacological target. To date, several therapeutic strategies and targets have been proposed to reduce clinical cardiotoxicities, among them iron-chelating drugs, β-blockers, renin-angiotensin-aldosterone system (RAAS) inhibitors, SGLT2 inhibitors, late inward sodium current (INa_L) selective inhibitors, phosphodiesterase-5 inhibitors, metabolic agents, and statins, as well as growth factors and hormones.

Dihydropyridine Ca^{2+}-channel blockers (amlodipine, felodipine) have been suggested as first-line agents in the case of fluoropyrimidine treatments, when chemotherapy-induced cardiotoxicities range from QT prolongation to hypertension and left ventricular dysfunction [102]. Cardiotoxic events were suggested to be mediated by vascular smooth muscle cells and, thus, dihydropyridine Ca^{2+}-channel blockers may exert direct vasodilatory effects via the arteriolar smooth muscle. As a side effect, there may be lower extremity edema, the frequency of which is dose-dependent and could be minimized by lowering the dose and by nocturnal administration [103]. On the other hand, non-dihydropyridine Ca^{2+} channel blockers are not indicated, due to drug-drug interactions and for the impact that they may have on the CYP3A4 system, which can lead to increased concentrations of the chemotherapeutic drug. Arterial hypertension is frequently reported (11–45%) in patients receiving VEGF inhibitors, such as bevacizumab and sunitinib. Ca^{2+} channel blockers are usually prescribed in these cases. In contrast, they should be used with caution in cases of arrhythmias, either supraventricular or ventricular, and in particular in bradyarrhythmias [96].

A recent review that summarized therapy-specific cardioprotective strategies only mentioned the chemotherapeutic class of proteasome inhibitors, confirming that, even though some information is available on how to treat these cardiotoxicities, robust data on primary cardioprotective strategies are lacking [104]. Indeed, compared to older classes of anti-cancer agents, proteasome inhibitors have only recently been introduced in clinical practice (the progenitor was approved by the FDA approval in 2008). This could be the main reason why an adequate estimation of their cardiotoxic effects is missing, and why the cellular and molecular mechanisms mediating the cardiotoxicity, and the role of T-type calcium channels, is still poorly explored. It appears clear though, that with the advancement of precision medicine and with the emerging of new classes of chemotherapy and targeted therapy drugs, there is an urgent need to develop novel strategies to mitigate adverse effects and to reduce clinical and subclinical cardiotoxicity.

6. T-Type Ca^{2+} Channels in Cancer

Due to their role in the regulation of cell-cycle progression, the aberrant expression and activity of T-type Ca^{2+} channels (Cav3.2) has been demonstrated and implicated in cancer. Thus, the expression of Cav3.X in cancer has been extensively reviewed [105]. We limit this report to a concise summary of the more evident literature.

According to Human Protein Atlas, 27% of glioblastoma biopsies express Cav3.2, while 82% express Cav3.1. Compared to commonly used established cell lines and the normal
brain, Cav3.2 expression is elevated in human glioblastoma and in glioblastoma stem cells that are resistant to radio and chemotherapy, and its deregulation correlates with worsened patient survival. An increase in intracellular calcium, modulated by Cav3.2 expression, has been shown to regulate glioblastoma cell proliferation [106,107]. Cav3.2 is upregulated in stages III and IV of medulloblastoma, the most common pediatric malignant brain tumor, and the level of expression correlates with aggressiveness, the occurrence of metastasis, and worsens clinical outcomes. Patients with high Cav3.2 levels show significantly reduced overall survival rates. Moreover, similar to the data learned from patients, the expression of upregulated Cav3.2 was increased in a mouse transgenic model of medulloblastoma tumor tissues compared to the control mice cerebellum tissues [108].

In prostate cancer, in samples harboring a mutant androgen receptor (AR) gene, which are, thus, resistant to the common therapy of AR blockers, the expression levels of Cav3.3 were significantly higher compared to samples negative for AR mutation. A further increase in Cav3.1 and Cav3.2 copy number variation rate was identified in neuroendocrine prostate cancer cells, which were highly metastatic and resistant to all available therapies, suggesting that T-type Ca\(^{2+}\) channels play a role in the progression from hormone-naive to neuroendocrine prostate cancer. Furthermore, the expression of Cav3.1 is associated with a poorer prognosis in earlier stages of the disease [109,110]. Data obtained from MCF-7 and MDA-MB-231 breast cancer cells showed high levels of mRNA for T-type Ca\(^{2+}\) channels, both Cav3.1 and 3.2, and expression was associated with hyperproliferation [111]. T-type Ca\(^{2+}\) channels are highly expressed in cutaneous melanoma where they play a crucial role in cell viability and induction of cell cycle progression. In particular, a progressive increase in the expression of Cav3.2 was found from normal skin to common nevi, to metastatic melanoma in human samples. Melanoma cells harboring mutations in the B-Raf proto-oncogene serine/threonine kinase (BRAF) gene, which is considered a genetic hallmark of >50% of melanoma, showed higher levels of Cav 3.1 and Cav 3.3 mRNA [112]. Immunocytochemistry, as well as qPCR and western blot analysis, revealed that Cav3.1 expression is also upregulated in the epithelial layers of human samples of Oral Squamous Cell Carcinoma (OSCC), and the expression levels correlated with the pathological grades (I vs II and III) and size of the tumor, and with the proliferative and anti-apoptotic potential. In contrast, the expression of Cav3.1 was markedly negative or weak in oral mucosa and epithelial dysplasia [113].

It is interesting to notice that, similar to T-type Ca\(^{2+}\) channels, sodium channels can also regulate cancer cell invasion, and their expression seems to facilitate cell motility, migration and invasiveness of cancer cells, and to correlate with metastatic potential [114–116]. This similarity may support speculation about a mechanistic relationship between the two types of ion channels. The ability of cancer cells to invade tissues is related to the presence of invasive structures, called invadopodia, that are functionally and morphologically similar to podosomes, that protrude at the edge of the cells, contact the extracellular matrix, and tune its degradation through metalloprotease activity, thus invading the surrounding tissue. Na\(^{+}\) and Ca\(^{2+}\) channels blockers have been found to reduce the formation of invadopodia, suggesting a possible common involvement [116,117]. These channels are both implicated in physiological membrane depolarization, and, from the biophysical point of view, they both rely on a window current that guarantees a constant inward flux of cations, even in relatively depolarized conditions (for the voltage-gated sodium channel the window current peaks at about −60 mV and may activate T-type calcium channels). In this sense, they both cooperate in increasing the intracellular calcium concentration that support the formation of invadopodia [116], and, thus, the cancer malignancy.

### 7. Therapeutic Strategies Aiming to Control T-Type Ca\(^{2+}\) Expression and Activity

From what has been described so far, it is intuitive that the control of the expression or activity of the T-type Ca\(^{2+}\) channels would be extremely advantageous in cancer therapy, whether calcium channels are expressed in cancer cells, or calcium channel expression is increased as a consequence of the antineoplastic therapy, as in CIPN. In the translational re-
search field, several methods, such as drug application, gene silencing, short interfering (or small interfering) RNA, and hairpin RNA, have been developed to reduce the CACNA1.X gene expression. The blockade of the channels through specific drugs or gene silencing lowered the proliferation rate, and dramatically reduced cell viability as cell death and apoptosis were promoted, both in breast cancer and in glioblastoma [106,111] (Table 2).

Table 2. Known compounds targeting T-type calcium channels studied in pre-clinical research or in clinical trials.

| Drug(s) | Cancer Type(s) | Model(s) | Reported Adverse Effects | References |
|---------|----------------|----------|--------------------------|------------|
| 5b, 6b, 6c, BK10040, 8, KYS05090, Amlodipine | Lung adenocarcinoma | A549 cell line | N.A. | [118] |
| Amlodipine | Human epidermoid carcinoma | A431 cell line | N.A. | [119] |
| Amlodipine | Uveal malignant melanoma | Cutaneous malignant melanoma cell lines and 3D cultures | N.A. | [120] |
| Amlodipine and doxorubicin, concomitant treatment | Gastric cancer | AGS and MKN45 cell lines | N.A. | [121] |
| Amlodipine and gemcitabine, concomitant treatment | Pancreatic ductal adenocarcinoma (PDAC) | Orthotopic Xenografts in mice and mouse model of PDAC | Not reported | [122] |
| Amlodipine and regorafenib, concomitant treatment | Metastatic colorectal cancer | Human patients | Not reported | [123] |
| Amlodipine and vincristine, concomitant treatment | Neuroblastoma | SH-SY5Y cell line | N.A. | [124] |
| Ascorbic Acid | Neuroblastoma-glioma | NG108-15 cell line | N.A. | [125] |
| C12 and C13 with cisplatin, concomitant treatment | Lung adenocarcinoma and human breast cancer | A549 and MDA-MB 231 cell lines | N.A. | [126] |
| KYS05041 KYS05042, KYS05043, KYS05046, KYS05047, KYS05048, KYS05055, KYS05056, KYS05057, KYS05065, KYS05080, KYS05085, KYS05089, KYS05090, KYS05090, 6a, 6c, 6d, 6f, 6g, 6h | Lung carcinoma, colon cancer, epidermoid carcinoma, malignant melanoma, ovarian cancer | A549, HCT-15, KB, SK-MEL-2, SKOV3 cell lines | N.A. | [25,118,127] |
| KYS05090 | Lung adenocarcinoma | Xenograft nude mice | Panting; inanimation; loss of locomotor activity; erosion, Diarrhea; soiled perineal region | [125] |
| KYS05090, 6a, 6c, 6d, 6f, 6g, 6h | Epithelial ovarian cancer | SK-OV-3 cell line | N.A. | [118] |
| Methanandamide | Neuroblastoma-glioma | NG108-15 cell line | N.A. | [125] |
| Mibefradil | Pancreatic cancer | Pancreatic cancer xenografts | Not reported | [126] |
| Mibefradil | Retinoblastoma, breast cancer, | Y79, WERI-Rb1 retinoblastoma, MCF7 cell lines | N.A. | [25] |
| Mibefradil | Glioma and neuroblastoma | U87MG, A172, U373, T98G, SNB19, U1242, U251 and SF767, C6, GIC, GliNS1, Gli79NS, Gli66NS, U3NNN-M NG108-15 and NIE-115 cell lines; primary glioblastoma cells (GBM-6, GBM-10) | N.A. | [25,125] |
| Drug(s)                        | Cancer Type(s)                              | Model(s)                                           | Reported Adverse Effects | References |
|-------------------------------|---------------------------------------------|----------------------------------------------------|--------------------------|------------|
| Mibefradil                    | Esophageal carcinoma                        | KYSE150, KYSE180, TE1, TE8                        | N.A.                     | [125]      |
| Mibefradil                    | Colon cancer                                | HCT116                                             | N.A.                     | [125]      |
| Mibefradil                    | Leukemia                                    | MOLT-4, Jurkat, Ball, HL-60, NB4, HEL, K-562, and U937 cell lines | N.A.                     | [125]      |
| Mibefradil                    | Glioma and glioblastome                     | Xenograft injection in mice                        | Not reported             | [125]      |
| Mibefradil                    | Ovarian cancer                              | HO8910, A2780 cell lines                          | N.A.                     | [125]      |
| Mibefradil                    | Ovarian cancer                              | Xenograft nude mice                                | Not reported             | [125]      |
| Mibefradil + Radiosurgery     | Glioblastoma                                | C6 xenograft in rat                                | Non reported             | [125]      |
| Mibefradil + temozolomide     | Glioblastoma                                | GBM xenograft                                     | Not reported             | [125]      |
| Mibefradil and carboplatin, timed sequential therapy | Ovarian cancer | In vivo xenografts (mouse model) | Not reported | [129] |
| Mibefradil and paclitaxel, timed sequential therapy | Breast cancer | In vivo xenografts (mouse model) | Not reported | [130] |
| Mibefradil and temozolomide, timed sequential therapy | Glioma | Human patients | Well tolerated (NCT01480050) | [131] |
| Nickel                        | Neuroblastoma-glioma                        | NG108-15 cell line                                | N.A.                     | [125]      |
| Nickel                        | Prostate cancer                             | LNCaP cell line                                   | N.A.                     | [125]      |
| Niguldipine                   | Glioma                                      | GIC, GliNS1, G179NS, and G166NS, U3NNN-MG cell lines | N.A.                     | [125]      |
| Niguldipine                   | Glioma                                      | Xenograft injection                               | Not reported             | [125]      |
| NNC 55-0396                   | Breast cancer                               | MCF-7 cell line                                   | N.A.                     | [111]      |
| NNC 55-0396                   | Human glioblastoma                          | Tumor xenograft mouse model                        | No side-effect on liver function | [132] |
| NNC 55-0396                   | Leukemia                                    | MOLT-4, Jurkat, Ball, HL-60, NB4, HEL, K-562, and U937 cell lines | N.A.                     | [125]      |
| NNC 55-0396                   | Ovarian cancer                              | HO8910, A2780 cell lines                          | N.A.                     | [125]      |
| Paclitaxel (+/−Nickel)        | Prostate cancer                             | LNCaP cell line                                   | N.A.                     | [125]      |
| Penfluoridol                  | Breast cancer, glioblastoma, pancreatic cancer, lung cancer, colon cancer | MDA-MB-231, HCC 1806, 4 Tl, GBM 43, GBM 10, GBM 44, GBM 28, GBM 14, T96G, U251 MG, U87MG, SJ-GBM2, CHLA-200, Panc-1, AsPC-1, BxPC-3m LCC, LL/2, CT26 cell lines | N.A. | [133] |
| Pimozide                      | Retinoblastoma, breast cancer, glioma       | Y79, WERI-Rb1 retinoblastoma, MCF7 breast cancer, C6 glioma cell lines | N.A. | [25] |
| TH-1177                       | Prostate cancer                             | Mice inoculated with PC3 cell line                 | No obvious toxicity, either in grossly or on histological examination. | [25] |
| Thapsigargin (+/−Nickel)      | Prostate cancer                             | LNCaP cell line                                   | N.A.                     | [125]      |
| TTA-P2                        | Glioma                                      | GIC, GliNS1, G179NS, and G166NS, U3NNN-MG cell lines | N.A. | [125] |
| TTA-P2                        | Glioma                                      | Xenograft injection                               | Not reported             | [125]      |

N.A. = Not Available due to the preclin.
In terms of cancer therapy, Ca\(^{2+}\) channel blockers are administered alone or as adjuvant drugs, synergistically combined with conventional chemotherapy (interlaced, or timed sequential therapy), where they may enhance the effectiveness of the therapy and represent a promising strategy for successful cancer treatment. In general, the idea of the timed sequential therapy is based on the concept that, by using a T-type Ca\(^{2+}\) channel blocker, the population of metabolically vulnerable cancer cells in the S-phase can be increased, which sensitizes cells to cytotoxic radiotherapy and chemotherapy (as in many cancers). This strategy was validated in a Phase 1b clinical trial (ClinicalTrials.gov identifier: NCT01480050) in which the T-type calcium channel blocker mibefradil was administered to synchronize the cells in the G1/S phase and, then, following its withdrawal, a standard chemotherapeutic cytotoxic agent temozolomide, active at S phase, was administered to kill the cells. Results were published in 2017, revealing that sequential treatment was safe and met the criteria for further evaluation of this regimen, despite the limitations of the study [131]. Mibefradil is a tetralol-derivative, non-dihydropyridine FDA-approved Ca\(^{2+}\) channel blocker, previously marketed for the treatment of hypertension and chronic angina pectoris, but withdrawn from the market worldwide in 1998, due to several reports of pharmacokinetic interactions with other drugs metabolized by CYP3A4 and 2D6. It was the first drug to be marketed as a specific T-type Ca\(^{2+}\) channel antagonist [134] as it blocks the T-types 10 to 30 times more potently than L-type Ca\(^{2+}\) channels, even though an inhibitory effect on the current flowing through the latter (IC\(_{\text{Ca}}\)) in vivo cannot be excluded [31]. It has been repurposed due to the fact it significantly inhibited cell growth and proliferation of glioblastoma stem cells and MCF-7 breast cancer cells. Moreover, it decreased cell viability in PC-3 cells, in an in-vitro model of neuroendocrine prostate cancer and in an in vivo model of glioblastoma, prolonging animal survival [106,109]. However, later reports showed that mibefradil can inhibit other ion channels, including the voltage-gated sodium, Ca\(^{2+}\)- and volume-activated chloride channels, and potassium (inward rectifier, delayed rectifier, and hERG) channels in the sinus and atrioventricular nodes, slowing conduction velocity [48,135].

Resistance in cancer therapy has been associated with hypoxia and HIF1alpha levels in cancer cells. This is true also for glioblastoma cells, in which hypoxia induced Cav3.2 and HIF1 and 2 expressions. Application of mibefradil not only significantly inhibited HIF1 and 2 expressions, but also inhibited the AKT/mTOR pro-survival pathway associated with cancer, and induced signaling changes related to the induction of cell-cycle arrest and apoptosis [106]. Other specific T-type Ca\(^{2+}\) channel blockers tested are the tetralol derivatives NNC 55-0396 and SB-209712. In particular, NNC 55-0396, an analog of mibefradil with higher blood-brain-barrier permeability, is more selective, and it blocks especially Cav3.1 and Cav3.2 with lower non-specific effects on L-type Ca\(^{2+}\) channels. Similar to mibefradil, NNC 55-0396 altered mitochondrial function, energy metabolism, induced cellular apoptosis in medulloblastoma cells [135], and caused cell-cycle arrest in a wide range of melanoma cells [136]. In some cases, the concentrations at which tetralols proved to be toxic for cultured cancer cells are higher than those required to block T-type Ca\(^{2+}\) channels. Thus, it has been proposed that the cancer cell death induced by tetralols was likely due to off-target actions. For example, in glioblastoma and melanoma, mibefradil and NNC 55-0396 seemed to activate IRE1 alpha (Inositol-Requiring Enzyme 1), and the unfolded protein response (UPR) system, leading to the mobilization of calcium from the endoplasmic reticulum, inducing apoptosis [107,112].

Anti-psychotic drugs, such as penfluridol and the structurally similar diphenylbutylpiperidine-derivative pimozide, block the calcium current with about tenfold higher selectivity for LVA over HVA channels, but they were also found to be potent inhibitors of hERG (the rapid component of the delayed rectifier), KvLQT1/minK (the slow component of the delayed rectifier), and Kv1.5 (ultra-rapid delayed rectifier) channels, even with much lower affinity, overall inducing QT interval prolongation [22,137]. Flunarizine, originally prescribed for migraine prophylaxis, is another proven T-type Ca\(^{2+}\) channel inhibitor whose selectivity is tissue-related. In smooth muscle cells and cardiomyocytes it does not select between L- and T-type, while in neuronal cells it preferentially blocks the T-type Ca\(^{2+}\)
channels with an equilibrium dissociation constant $K_D$ 4-fold higher [138]. A small cyclic peptide named PnCS1 was found to inhibit the three members of the Cav3 family with the same potency. By using a cryo-EM approach, it was established that the cyclic peptide locates in the central pore, between the selectivity filter and the intracellular gate of the Cav3.1 channel, and molecular dynamics simulations revealed remarkable stability of the interaction [139]. The pyridyl amide TTA-A2 has a 300-fold higher affinity for T-type compared to others channels, revealing it to be a potent blocker, and was demonstrated to be efficient in inducing cell death in lung adenocarcinoma cells, and reducing colony formation, a process at the basis of metastatic colonization. In particular, TTA-A2 treatment not only blocked Cav3.X, but also down-regulated its mRNA expression [140]. Similarly, a novel series of N3- substituted dihydropyrimidines has been developed, two of which, named C12 and C13, are highly selective for Cav3.2 and revealed anticancer activity when applied alone or in combination with cisplatin and etoposide on A549 cell line (lung adenocarcinoma) and on a human breast cancer cell line (MDA-MB 231), showing synergistic activity. In silico studies on the same compounds suggested a low level of cardiac toxicity, as these drugs did not block hERG channels, essential for cardiomyocyte repolarization [126].

On the other hand, T-type Ca$^{2+}$ channels may also be a pharmacotherapeutic target to reduce neuronal sensitivity, with the potential for the reversal of chemotherapy-induced peripheral neurotoxicity associated with antineoplastics (see CIPN) [141,142]. Suvecaltamide is another potent and selective modulator of T-type Ca$^{2+}$ channels with a high affinity for the inactivated channel conformation. Its administration in a rat model of CIPN provoked an increase in nerve conduction velocity in caudal and sciatic nerves without interacting with BTZ-induced proteasome inhibition activity, and suggested that suvecaltamide does not block or attenuate BTZ anti-tumor activity [142]. Other recent developments in the discovery of novel classes of T-type Ca$^{2+}$ channel blockers of pain, including their analgesic effects in animal models, and in clinical trials, have been proposed by Snutch and Zamponi in 2017 [16]. Despite this plethora of new molecules, most of the T-type Ca$^{2+}$ channel blockers still interfere with other protein functions, in particular ion channels.

8. Conclusions

The role of T-type Ca$^{2+}$ channels have naturally been associated with membrane excitability of the central and peripheral neurons, and of the pacemaker cells in the cardiac and smooth muscle tissues. As their activation is voltage-dependent, they promote action potential firing by amplifying weak depolarizing stimuli, driving the membrane potential towards the excitability threshold of other voltage-gated channels. Nevertheless, thanks to the “power” of the window current, they also contribute also to activating biochemical signals that initiate multiple physiological events, even in non-excitable cells, most notably cancer cells [143]. In this context, they are linked to cell-cycle progression, proliferation, survival, migration, and supporting malignant growth. Thus, their activity has to be finely regulated and several pharmacological T-type Ca$^{2+}$ channel blockers have been developed to be used either in the cardiovascular and the oncology fields as chemotherapeutics or in adjuvant therapy. However, precisely because of the relevant physiological and pathophysiological roles of these channels, and also because the drugs have been revealed not to be thoroughly specific, caution is needed in their use as the final effect could be a mixture of on-target and off-target actions. Besides the studied cardiotoxicity, the risk of pathological arrhythmias is always a consideration. Thus, the full exploration of the therapeutic potential of targeting Cav3 channels would benefit from the development of ligands with high potency and selectivity, and from the implementation of cardiomyocyte electrophysiological studies.

Author Contributions: Conceptualization, D.M., A.F., S.C. and I.R.; writing—original draft preparation, D.M., A.F., S.C. and G.A.M.; writing—review and editing, D.M., A.F., S.C. and I.R.; supervision, C.P. and I.R. All authors have read and agreed to the published version of the manuscript.
Funding: This research was funded by the University of Milano-Bicocca, 2021-ATE-0069.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: The Authors acknowledge the University of Milano-Bicocca for funding and Conor McClenaghan of the Center for Advanced Biotechnology and Medicine, and Departments of Pharmacology & Medicine, Rutgers University, Piscataway, NJ for the language revision.

Conflicts of Interest: The authors declare no conflict of interest.

List of Abbreviations in Alphabetical Order

| Abbreviation | Description                          |
|--------------|--------------------------------------|
| AID          | Alpha-interaction domain             |
| AR           | Androgen receptor                    |
| BIPN         | Bortezomib-induced peripheral neuropathy |
| BRAF         | B-Raf proto-oncogene serine/threonine kinase |
| BTZ          | Bortezomib                           |
| Ca^{2+}      | Calcium ion                          |
| CFZ          | Carfilzomib                          |
| CIPN         | Chemotherapy-induced peripheral neuropathy |
| Cryo-EM      | Cryogenic electron microscopy        |
| CYP          | Cytochrome P450                       |
| DRGs         | Dorsal root ganglia                  |
| ER           | Endoplasmic reticulum                |
| HEK          | Human embryonic kidney               |
| hERG         | human Ether-a-go-go-Related Gene      |
| HVA          | High-voltage-activated               |
| ICaL         | L-type calcium current               |
| ICaT         | T-type calcium current               |
| INaL         | Late sodium current                  |
| IRE          | Inositol-requiring enzyme            |
| K^{+}        | Potassium ion                        |
| KD           | Dissociation constant                |
| LA           | Low-voltage-activated                |
| Na^{+}       | Sodium ion                           |
| NFAT         | Nuclear factor of activated T-cells  |
| OSCC         | Oral Squamous Cell Carcinoma         |
| PNG          | Prenylnaringenin                     |
| qPCR         | Quantitative PCR                     |
| RAAS         | Renin-angiotensin-aldosterone system |
| SGLT2        | Sodium-glucose transporter 2         |
| TNF          | Tumor Necrosis Factor                |
| TRP          | Transient receptor potential         |
| UPR          | Unfolded protein response            |
| UPS          | Ubiquitin-proteasome system          |
| USP5         | Ubiquitin-specific cysteine protease 5 |
| VEGF         | Vascular-Endothelial Growth Factor   |

References

1. Ono, K.; Iijima, T. Pathophysiological Significance of T-type Ca^{2+} Channels: Properties and Functional Roles of T-type Ca^{2+} Channels in Cardiac Pacemaking. *J. Pharmacol. Sci.* 2005, 99, 197–204. [CrossRef] [PubMed]
2. Perez-Reyes, E. Molecular Physiology of Low-Voltage-Activated T-type Calcium Channels. *Physiol. Rev.* 2003, 83, 117–161. [CrossRef] [PubMed]
3. Todorovic, S.M.; Jevtovic-Todorovic, V. The role of T-type calcium channels in peripheral and central pain processing. *CNS Neurol. Disord. Drug Targets* 2006, 5, 639–653. [CrossRef] [PubMed]
4. Bijlenga, P.; Liu, J.-H.; Espinos, E.; Haenggeli, C.-A.; Fischer-Lougede, J.; Bader, C.R.; Bernheim, L. T-type α1H Ca²⁺ channels are involved in Ca²⁺ signaling during terminal differentiation (fusion) of human myoblasts. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 7627-7632. [CrossRef] [PubMed]

5. Huguenard, J.R. Low-threshold calcium currents in central nervous system neurons. *Annu. Rev. Physiol.* **1996**, *58*, 329-348. [CrossRef]

6. Hansen, P.B.L. Functional importance of T-type voltage-gated calcium channels in the cardiovascular and renal system: News from the world of knockout mice. *Am. J. Physiol. Regul. Interc. Comp. Physiol.* **2015**, *308*, R227-R237. [CrossRef]

7. Carbone, E.; Calorio, C.; Vandael, D.H.F. T-type channel-mediated neurotransmitter release. *Pflug. Arch. Eur. J. Physiol.* **2014**, *466*, 677-687. [CrossRef]

8. Cribbs, L.L.; Lee, J.H.; Yang, J.; Satin, J.; Zhang, Y.; Daud, A.; Barclay, J.; Williamson, M.P.; Fox, M.; Rees, M.; et al. Cloning and characterization of alpha1H from human heart, a member of the T-type Ca²⁺ channel gene family. *Circ. Res.* **1998**, *83*, 103-109. [CrossRef]

9. Perez-Reyes, E.; Cribbs, L.L.; Daud, A.; Lacerda, A.E.; Barclay, J.; Williamson, M.P.; Fox, M.; Rees, M.; Lee, J.H. Molecular characterization of a neuronal low-voltage-activated T-type calcium channel. *Nature* **1998**, *391*, 896-900. [CrossRef]

10. Perez-Reyes, E.; Cribbs, L.L.; Lacerda, A.E.; Pereverzev, A.; Klockner, U.; Schneider, T.; Perez-Reyes, E. Cloning and expression of a novel member of the low voltage-activated T-type calcium channel family. *J. Neurosci.* **1999**, *19*, 1912-1921. [CrossRef]

11. Weiss, N.; Zamponi, G.W. T-type calcium channels: From molecule to therapeutic opportunities. *Int. J. Biochem. Cell Biol.* **2019**, *108*, 34-39. [CrossRef] [PubMed]

12. Shah, K.; Seeley, S.; Schulz, C.; Fisher, J.; Rao, S.G. Calcium Channels in the Heart: Disease States and Drugs. *Cells* **2022**, *11*, 943. [CrossRef] [PubMed]

13. Klöckner, U.; Lee, J.H.; Cribbs, L.L.; Daud, A.; Hescheler, J.; Perez-Reyes, E.; Schneider, T. Comparison of the Ca²⁺ currents induced by expression of three cloned alpha1 subunits, alpha1G, alpha1H and alpha1I, of low-voltage-activated T-type Ca²⁺ channels. *Eur. J. Neurosci.* **1999**, *11*, 4171-4178. [CrossRef] [PubMed]

14. Lee, J.H.; Daud, A.N.; Cribbs, L.L.; Lacerda, A.E.; Pereverzev, A.; Perez-Reyes, E. Nickel block of three cloned T-type calcium channels: Low concentrations selectively block α1H. *Biophys. J.* **1999**, *77*, 3034-3042. [CrossRef]

15. Lory, P.; Nicole, S.; Monteil, A. Neuronal Cav3 channelopathies: Recent progress and perspectives. *Pflügers Arch.-Eur. J. Physiol.* **2020**, *472*, 831-844. [CrossRef]

16. Snutch, T.P.; Zamponi, G.W. Recent advances in the development of T-type calcium channel blockers for pain intervention. *Br. J. Pharmacol.* **2018**, *175*, 2375-2383. [CrossRef]

17. Kopecky, B.J.; Liang, R.; Bao, J. T-type calcium channel blockers as neuroprotective agents. *Pflug. Arch. Eur. J. Physiol.* **2014**, *466*, 757-765. [CrossRef]

18. Scott, V.E.; Vortherms, T.A.; Niforatos, W.; Swensen, A.M.; Neelands, T.; Milicic, I.; Banfor, P.N.; King, A.; Zhong, C.; Simler, G.; et al. A-1048400 is a novel, orally active, state-dependent neuronal calcium channel blocker that produces dose-dependent inhibition of T-type calcium channels by neuroleptics. *J. Neurosci.* **2002**, *22*, 396-403. [CrossRef] [PubMed]

19. Traboulis, A.; Chemin, J.; Kupfer, E.; Nargeot, J.; Lory, P. T-type calcium channels are inhibited by fluoxetine and its metabolite norfluoxetine. *J. Neurosci.* **2000**, *20*, 2747-2755. [CrossRef] [PubMed]

20. Bladen, C.; Hamid, J.; Souza, I.A.; Zamponi, G.W. Block of T-type calcium channels by protoxins I and II. *Mol. Brain* **2010**, *3*, 1. [CrossRef] [PubMed]

21. Bergson, P.; Lipkind, G.; Lee, S.P.; Duban, M.E.; Hanck, D.A. Verapamil block of T-type calcium channels. *Mol. Pharmacol.* **2011**, *79*, 411-419. [CrossRef]

22. Ono, K.; Iijima, T. Cardiac T-type Ca²⁺ channels in the heart. *J. Mol. Cell. Cardiol.* **2010**, *48*, 65-70. [CrossRef] [PubMed]
32. Vassort, G.; Talavera, K.; Alvarez, J.L. Role of T-type Ca²⁺ channels in the heart. Cell Calcium 2006, 40, 205–220. [CrossRef] [PubMed]
33. Senatore, A.; Spafford, J.D. Gene transcription and splicing of T-type channels are evolutionarily-conserved strategies for regulating channel expression and gating. PLoS ONE 2012, 7, e37409. [CrossRef]
34. Ferron, L.; Capuano, V.; Derouaux, E.; Coulombe, A.; Renaud, J.-F. Functional and molecular characterization of a T-type Ca²⁺ channel during fetal and postnatal rat heart development. J. Mol. Cell. Cardiol. 2002, 34, 533–546. [CrossRef] [PubMed]
35. Niwa, N.; Yasui, K.; Opphol, T.; Takemura, H.; Shimizu, A.; Horiba, M.; Lee, J.-K.; Honjo, H.; Kaniya, K.; Kodama, I. Cav3.2 subunit underlies the functional T-type Ca²⁺ channel in murine hearts during the embryonic period. Am. J. Physiol. Heart Circ. Physiol. 2004, 286, H2257–H2263. [CrossRef]
36. Benitah, J.P.; Gomez, A.M.; Fauconnier, J.; Kerfant, B.G.; Perrier, E.; Vassort, G.; Richard, S. Voltage-gated Ca²⁺ currents in the human pathophysiologic heart: A review. Basic Res. Cardiol. 2002, 97, 111–118. [CrossRef]
37. Monteil, A.; Chemin, J.; Bourinet, E.; Mennessier, G.; Lory, P.; Nargeot, J. Molecular and Functional Properties of the Human αG Subunit That Forms T-type Calcium Channels. J. Biol. Chem. 2000, 275, 6909–6100. [CrossRef]
38. Chandler, N.J.; Greener, I.D.; Tellez, J.O.; Inada, S.; Musa, H.; Molenaar, P.; DiFrancesco, D.; Baruscotti, M.; Longhi, R.; Anderson, R.H.; et al. Molecular architecture of the human sinus node: Insights into the function of the cardiac pacemaker. Circulation 2009, 119, 1562–1575. [CrossRef]
39. Mädle, A.; Linhartová, K.; Koza, J. Effects of the T-type calcium channel blockade with oral mibebradil on the electrophysiologic properties of the human heart. Med. Sci. Monit. 2001, 7, 74–77. [PubMed]
40. Nuss, H.B.; Houser, S.R. T-type Ca²⁺ current is expressed in hypertrophied adult feline left ventricular myocytes. Circ. Res. 1993, 73, 777–782. [CrossRef]
41. Martinez, M.L.; Heredia, M.P.; Delgado, C. Expression of T-type Ca²⁺ Channels in Ventricular Cells from Hypertrophied Rat Hearts. J. Mol. Cell. Cardiol. 1999, 31, 1617–1625. [CrossRef]
42. Chiang, C.S.; Huang, C.H.; Chieng, H.; Chang, Y.-T.; Chang, D.; Chen, J.-J.; Chen, Y.-C.; Chen, Y.-H.; Shin, H.-S.; Campbell, K.P.; et al. The CaV3.2 T-Type Ca²⁺ Channel Is Required for Pressure Overload-Induced Cardiac Hypertrophy in Mice. Circ. Res. 2009, 104, 522–530. [CrossRef]
43. Petersen, M.; Wagner, G.; Pierau, F.K. Modulation of calcium-currents by capsaicin in a subpopulation of sensory neurones of guinea pig. Naunyn. Schmiedebergs. Arch. Pharmacol. 1989, 339, 184–191. [CrossRef] [PubMed]
44. Haberberger, R.V.; Barry, C.; Dominguez, N.; Matusica, D. Human Dorsal Root Ganglia. Front. Cell. Neurosci. 2019, 13, 271. [CrossRef] [PubMed]
45. Todorovic, S.M.; Jevtovic-Todorovic, V.; Meyenburg, A.; Mennerick, S.; Perez-Reyes, E.; Nelson, M.T.; Joksovic, P.M.; Perez-Reyes, E.; Todorovic, S.M. The endogenous redox agent L-cysteine induces T-type Ca²⁺ channel-dependent sensitization of a novel subpopulation of rat peripheral nociceptors. J. Neurosci. 2005, 25, 8766–8775. [CrossRef] [PubMed]
46. Cai, S.; Gomez, K.; Moutal, A.; Khanna, R. Targeting T-type/CaV3.2 channels for chronic pain. Transl. Res. 2021, 234, 20–30. [CrossRef]
47. Feng, X.; Zhang, L.; Ma, L.-X.; Jiao, C.; Wang, H.-X.; Zeng, F.; Zhou, X.-Y.; Cheng, X.-E.; Zhu, M.-Y.; Zhang, D.-Y.; Jiang, C.-Y.; et al. Nerve injury elevates functional Cav3.2 channels in superficial spinal dorsal horn. Mol. Pain 2019, 15, 1744806918836569. [CrossRef]
48. Gomez, K.; Calderón-Rivera, A.; Sandoval, A.; González-Ramírez, R.; Vargas-Parada, A.; Ojeda-Alonso, J.; Granados-Soto, V.; Delgado-Lezama, R.; Flexi, R. Cdk5-Dependent Phosphorylation of CaV3.2 T-Type Channels: Possible Role in Nerve Ligation-Induced Neuropathic Allodynia and the Compound Action Potential in Primary Afferent C Fibers. J. Neurosci. 2019, 40, 283–296. [CrossRef]
49. Garcia-Caballero, A.; Gadotti, V.M.; Stemkowski, P.; Weiss, N.; Souza, I.A.; Hodgkinson, V.; Bladen, C.; Chen, L.; Hamid, J.; Pizzoccaro, A.; et al. The deubiquitinating enzyme USP5 modulates neuropathic pain and inflammatory pain by enhancing Cav3.2 channel activity. Neuron 2014, 83, 1144–1158. [CrossRef] [PubMed]
50. Tomita, S.; Sekiguchi, F.; Kusanami, Y.; Naoe, K.; Tsutoba, M.; Wake, H.; Nishibori, M.; Kabawata, A. Cav3.2 overexpression in L4 dorsal root ganglion neurons after L5 spinal nerve cutting involves Egr-1, USP5 and HMGB1 in rats: An emerging signaling pathway for neuropathic pain. Eur. J. Pharmacol. 2020, 888, 173587. [CrossRef] [PubMed]
51. Flatters, S.J.L.; Dougherty, P.M.; Colvin, L.A. Clinical and preclinical perspectives on Chemotherapy-Induced Peripheral Neuropathy (CIPN): A narrative review. Br. J. Anaesth. 2017, 119, 737–749. [CrossRef]
52. Zajaczkowska, R.; Kocot-Kępka, M.; Leppert, W.; Wrzosek, A.; Mika, J.; Wordliczek, J. Mechanisms of chemotherapy-induced peripheral neuropathy. Int. J. Mol. Sci. 2019, 20, 1451. [CrossRef] [PubMed]
53. Staff, N.P.; Fehrenbacher, J.C.; Caillaud, M.; Damaj, M.I.; Segal, R.A.; Rieger, S. Pathogenesis of paclitaxel-induced peripheral neuropathy: A current review of in vitro and in vivo findings using rodent and human model systems. Exp. Neurol. 2020, 324, 113121. [CrossRef]
56. Nyrop, K.A.; Deal, A.M.; Shachar, S.S.; Basch, E.; Reeve, B.B.; Choi, S.K.; Lee, J.T.; Wood, W.A.; Anders, C.K.; Carey, L.A.; et al. Patient-Reported Toxicities During Chemotherapy Regimens in Current Clinical Practice for Early Breast Cancer. *Oncologist* 2019, 24, 762–771. [CrossRef] [PubMed]

57. Li, Y.; Tatsui, C.E.; Rhines, L.D.; North, R.Y.; Harrison, D.S.; Cassidy, R.M.; Johansson, C.A.; Kosturakis, A.K.; Edwards, D.D.; Zhang, H.; et al. Dorsal root ganglion neurons become hyperexcitable and increase expression of voltage-gated T-type calcium channels (Cav3.2) in paclitaxel-induced peripheral neuropathy. *Pain* 2017, 158, 417–429. [CrossRef]

58. Adams, J.; Palombella, V.J.; Sausville, E.A.; Johnson, J.; Destree, A.; Lazarus, D.D.; Maas, J.; Pien, C.S.; Prakash, S.; Elliott, P.J. Proteasome inhibitors: A novel class of potent and effective antitumor agents. *Cancer Res.* 1999, 59, 2615–2622.

59. Pipardi, B.; Ling, Y.-H.; Liebes, L.; Muggia, F.; Perez-Soler, R. Bortezomib: Understanding the Mechanism of Action. *Mol. Cancer Ther.* 2011, 10, 2029–2030. [CrossRef]

60. Troupakos, I.P.; Sesti, F.; Tsakiri, E.; Gorgoulis, V.G. Non-enzymatic post-translational protein modifications and proteostasis network deregulation in carcinogenesis. *J. Proteom.* 2013, 92, 274–298. [CrossRef]

61. Argyriou, A.A.; Cavaletti, G.; Bruna, J.; Kyrtsis, A.P.; Kalofonos, H.P. Bortezomib-induced peripheral neurotoxicity: An update. *Arch. Toxicol.* 2014, 88, 1669–1679. [CrossRef] [PubMed]

62. Pancheri, E.; Guglielmi, V.; Willeczynski, G.M.; Malatesta, M.; Tonin, P.; Tomelleri, G.; Nowis, D.; Vattemi, G. Non-Hematologic Toxicity of Bortezomib in Multiple Myeloma: The Neuromuscular and Cardiovascular Adverse Effects. *Cancers* 2020, 12, 2540. [CrossRef] [PubMed]

63. Ling, Y.H.; Liebes, L.; Ng, B.; Buckley, M.; Elliott, P.J.; Adams, J.; Jiang, J.-D.; Muggia, F.M.; Perez-Soler, R. PS-341, a Novel Proteasome Inhibitor, Induces Bel-2 Phosphorylation and Cleavage in Association with G2-M Phase Arrest and Apoptosis. *Mol. Cancer Ther.* 2002, 1, 841–849. [CrossRef] [PubMed]

64. Cavaletti, G.; Giglardi, A.; Canta, A.; Rigamonti, L.; Rodriguez-Menendez, V.; Ceresa, C.; Marmiroli, P.; Bossi, M.; Oggoni, N.; D’Incalci, M.; et al. Bortezomib-induced peripheral neurotoxicity: A neurophysiological and pathological study in the rat. *Exp. Neurol.* 2007, 204, 317–325. [CrossRef] [PubMed]

65. Bruna, J.; Udina, E.; Ale, A.; Vilches, J.J.; Vynckier, A.; Monbaliu, J.; Silverman, L.; Navarro, X. Neurophysiological, histological, and immunohistochemical characterization of bortezomib-induced neuropathy in mice. *Exp. Neurol.* 2010, 223, 599–608. [CrossRef] [PubMed]

66. Tomita, S.; Sekiguchi, F.; Deguchi, T.; Miyazaki, T.; Ikeda, Y.; Tsubota, M.; Yoshida, S.; Nguyen, H.D.; Okada, T.; Toyooka, N.; et al. Critical role of Cav3.2 T-type calcium channels in the peripheral neuropathy induced by bortezomib, a proteasome-inhibiting chemotherapeutic agent, in mice. *Toxicology* 2019, 413, 33–39. [CrossRef]

67. Dimopoulos, M.A.; Richardson, P.G.; Moreau, P.; Anderson, K.C. Current treatment landscape for relapsed and/or refractory multiple myeloma. *Nat. Rev. Clin. Oncol.* 2015, 12, 42–54. [CrossRef]

68. Tsakiri, E.N.; Terpos, E.; Papanagnou, E.-D.; Kastritis, E.; Brieudes, V.; Halabalaki, M.; Bagratuni, T.; Florea, B.I.; Overkleeft, H.S.; Scorrano, L.; et al. Milder degenerative effects of Carfilzomib vs. Bortezomib in the Drosophila model: A link to clinical adverse events. *Sci. Rep.* 2017, 7, 17802. [CrossRef] [PubMed]

69. Siegel, D.; Martin, T.; Noooka, A.; Harvey, R.D.; Vij, R.; Niesvizky, R.; Badros, A.Z.; Jagannath, S.; McCulloch, L.; Rajangam, K.; et al. Integrated safety profile of single-agent carfilzomib: Experience from 526 patients enrolled in 4 phase II clinical studies. *Haematologica* 2013, 98, 1753. [CrossRef]

70. Oruciolo, E.; Gabriele, B.; Cecconi, N.; Galimberti, S.; Versari, D.; Cervetti, G.; Salvetti, A.; Petrini, M. Unexpected cardiotoxicity in haematological bortezomib treated patients. *Br. J. Haematol.* 2007, 138, 396–397. [CrossRef]

71. Honton, B.; Despas, F.; Dumonteil, N.; Rouvellat, C.; Roussel, M.; Carrie, D.; Galinier, M.; Montastruc, J.L.; Pathak, A. Bortezomib and heart failure: Case-report and review of the French Pharmacovigilance database. *Fundam. Clin. Pharmacol.* 2014, 28, 349–352. [CrossRef] [PubMed]

72. Herrmann, J.; Ciechanover, A.; Lerman, L.O.; Lerman, A. The ubiquitin–proteasome system in cardiovascular diseases—A hypothesis extended. *Cardiovasc. Res.* 2004, 61, 11–21. [CrossRef] [PubMed]

73. Kornitzer, D.; Ciechanover, A. Modes of regulation of ubiquitin-mediated protein degradation. *J. Cell. Physiol.* 2000, 182, 1–11. [CrossRef]

74. Ciechanover, A.; Orian, A.; Schwartz, A.L. The ubiquitin-mediated proteolytic pathway: Mode of action and clinical implications. *J. Cell. Biochem.* 2000, 77, 40–51. [CrossRef]

75. Schulman, B.A.; Harper, J.W. Ubiquitin-like protein activation by E1 enzymes: The apex for downstream signalling pathways. *Nat. Rev. Mol. Cell Biol.* 2009, 10, 319–331. [CrossRef]

76. Brannigan, J.A.; Dodson, G.; Duggleby, H.J.; Moody, P.C.; Smith, J.L.; Tomchick, D.R.; Murzin, A.G. A protein catalytic framework with an N-terminal nucleophile is capable of self-activation. *Nature* 1995, 378, 416–419. [CrossRef]

77. Unno, M.; Mizushima, T.; Morimoto, Y.; Tomisugi, Y.; Tanaka, K.; Yasuoka, N.; Tsukihara, T. The structure of the mammalian 20S proteasome at 2.75 Å resolution. *Nat. Struct. Mol. Biol.* 1995, 2, 416–419. [CrossRef]

78. Voges, D.; Zwickl, P.; Baumeister, W. The 26S Proteasome: A Molecular Machine Designed for Controlled Proteolysis. *Annu. Rev. Biochem.* 1999, 68, 1015–1068. [CrossRef]

79. Kaplan, G.S.; Torcun, C.C.; Grune, T.; Ozer, N.K.; Karademir, B. Proteasome inhibitors in cancer therapy: Treatment regimen and peripheral neuropathy as a side effect. *Free Radic. Biol. Med.* 2017, 103, 1–13. [CrossRef]
80. Kato, M.; Ogura, K.; Miake, J.; Sasaki, N.; Taniguchi, S.-I.; Igawa, O.; Yoshida, A.; Hoshikawa, Y.; Murata, M.; Nanba, E.; et al. Evidence for proteasomal degradation of Kv1.5 channel protein. *Biochem. Biophys. Res. Commun.* 2005, 337, 343–348. [CrossRef] [PubMed]

81. Chapman, H.; Ramstrom, C.; Korthonen, L.; Laine, M.; Wann, K.T.; Lindholm, D.; Pasternack, M.; Tornquist, K. Downregulation of the HERG (KCNH2) K+ channel by ceramide: Evidence for ubiquitin-mediated lysosomal degradation. *J. Cell Biol.* 2005, 168, 5325–5334. [CrossRef] [PubMed]

82. Zolk, O.; Schenke, C.; Sarikas, A. The ubiquitin–proteasome system: Focus on the heart. *Cardiovasc. Res.* 2006, 70, 410–421. [CrossRef] [PubMed]

83. Gong, Q.; Keeney, D.R.; Molinari, M.; Zhou, Z. Degradation of trafficking-defective long QT syndrome type II mutant channels by the ubiquitin-proteasome pathway. *J. Biol. Chem.* 2005, 280, 19419–19425. [CrossRef] [PubMed]

84. Mihic, A.; Chauhan, V.S.; Gao, X.; Oudit, G.Y.; Tsushima, R.G. Trafficking defect and proteasomal degradation contribute to the phenotype of a novel KCNH2 long QT syndrome mutation. *PLoS ONE* 2011, 6, e18273. [CrossRef] [PubMed]

85. Calcaterra, N.E.; Hoeppner, D.J.; Wei, H.; Jaffe, A.E.; Maher, B.J.; Barrow, J.C. Schizophrenia-Associated hERG channel Kv11.1-3.1 Exhibits a Unique Trafficking Deficit that is Rescued Through Proteasome Inhibition for High Throughput Screening. *Sci. Rep.* 2016, 6, 19976. [CrossRef]

86. Choi, S.W.; Choi, S.W.; Jeon, Y.K.; Moon, S.-H.; Zhang, Y.-H.; Kim, S.J. Suppression of hERG K+ current and cardiac action potential prolongation by 4-hydroxynonenal via dual mechanisms. *Redox Biol.* 2018, 19, 190–199. [CrossRef]

87. Van Bemmelen, M.X.; Rougier, J.-S.; Gavillet, B.; Apotheloz, F.; Daidié, D.; Tatemyama, M.; Rivolta, I.; Thomas, M.A.; Kass, R.S.; Staub, O.; et al. Cardiac voltage-gated sodium channel Nav1.5 is regulated by Nedd4-2 mediated ubiquitination. *Circ. Res.* 2004, 95, 284–291. [CrossRef] [PubMed]

88. Kang, L.; Zheng, M.Q.; Morishima, M.; Wang, Y.; Kaku, T.; Ono, K. Bepridil up-regulates cardiac Na+ channels as a long-term effect by blunting proteasome signals through inhibition of calmodulin activity. *Br. J. Pharmacol.* 2009, 157, 404–414. [CrossRef]

89. Rougier, J.S.; Gavillet, B.; Abriel, H. Proteasome inhibitor (MG132) rescues Nav1.5 protein content and the cardiac sodium current in dysoxthine-deficient mdx5cv mice. *Front. Physiol.* 2013, 4, 51. [CrossRef] [PubMed]

90. Morais, E.R.; Oliveira, K.C.; de Paula, R.G.; Ornelas, A.M.M.; Moreira, É.B.C.; Badoco, F.R.; Magalhães, L.G.; Verjovski-Almeida, S.; Rodrigues, V. Effects of proteasome inhibitor MG-132 on the parasite Schistosoma mansoni. *PLoS ONE* 2017, 12, e0184192. [CrossRef]

91. Magdy, T.; Burmeister, B.T.; Burridge, P.W. Validating the pharmacogenomics of chemotherapy-induced cardiotoxicity: What is missing? *Pharmacol. Ther.* 2016, 168, 113–125. [CrossRef] [PubMed]

92. Miolo, G.M.; la Mura, N.; Nigri, P.; da Ronch, L.; Viel, E.; Veronesi, A.; Lestuzzi, C. The cardiotoxicity of the anticancer therapeutic agent bortezomib. *Biochem. Biophys. Res. Commun.* 2005, 337, 284–291. [CrossRef] [PubMed]

93. Bugajski, M.; et al. Cardiotoxicity of the anticancer agent bortezomib. *Am. J. Pathol.* 2009, 176, 2658–2668. [CrossRef] [PubMed]

94. Habino, B.B.; Patel, D.; Wu, X. Molecular Mechanisms and Strategies for Cardioprotection. *Front. Cardiovasc. Med.* 2022, 9, 847012. [CrossRef] [PubMed]

95. Schlitt, A.; Jordan, K.; Vordermark, D.; Schwamborn, J.; Langer, T.; Thomssen, C. Cardiotoxicity and oncological treatments. *JACC CardioOncology State-of-the-Art Review.* 2018, 4, 19–37. [CrossRef] [PubMed]

96. Omland, T.; Heck, S.L.; Gulati, G. The Role of Cardioprotection in Cancer Therapy Cardiotoxicity: JACC CardioOncology State-of-the-Art Review. *JACC CardioOncology* 2022, 4, 19–37. [CrossRef] [PubMed]

97. Pross, S.B.; Gilda, J.E.; Ping, P.; Gomes, A.V. Regulation of cardiac proteasomes by ubiquitination, SUMOylation, and beyond. *J. Mol. Cell. Cardiol.* 2014, 71, 32–42. [CrossRef]

98. Panek, A.; Seto, T.; Pagano, M.; Cittadini, A. Role of the ubiquitin proteasome system in the heart. *Circ. Res.* 2013, 112, 1046–1058. [CrossRef]

99. Pandey, A.K.; Singhi, E.K.; Arroyo, J.P.; Ikizler, T.A.; Gould, E.R.; Brown, J.; Beckman, J.A.; Harrison, D.G.; Moslehi, J. Mechanisms of VEGF-Inhibitor-Associated Hypertension and Vascular Disease. *Hypertension* 2018, 71, e1. [CrossRef] [PubMed]

100. Rao, V.U.; Reeves, D.J.; Chugh, A.R.; O’Quinn, R.; Bradley, M.G.; Raghavendra, M.; Dent, S.; Barac, A.; Lenihan, D. Clinical Approach to Cardiovascular Toxicity of Oral Antineoplastic Agents: JACC State-of-the-Art Review. *J. Am. Coll. Cardiol.* 2021, 77, 2693–2716. [CrossRef]

101. Visa, A.; Sallan, M.C.; Maïques, O.; Alza, L.; Talavera, E.; Lopez-Ortega, R.; Santacana, M.; Herreros, J.; Canti, C. T-Type Ca v 3.1 Channels Mediate Progressive and Chemotherapeutic Resistance in Glioblastoma. *Cancer Res.* 2019, 79, 1857–1868. [CrossRef]
108. Maklad, A.; Sedeeq, M.; Milevski, M.J.G.; Azimi, I. Calcium Signalling in Medulloblastoma: An In Silico Analysis of the Expression of Calcium Regulating Genes in Patient Samples. *Genes 2021*, *12*, 1329. [CrossRef]
109. Silvestri, R.; Pucci, P.; Venalainen, E.; Matheau, C.; Mather, R.; Chandler, S.; Aceto, R.; Rigas, S.H.; Wang, Y.; Riedtolf, K.; et al. T-type calcium channels drive the proliferation of androgen-receptor negative prostate cancer cells. *Prostate 2019*, *79*, 1580–1586. [CrossRef]
110. Mariot, P.; Vanoverbergh, K.; Lalevée, N.; Rossier, M.F.; Prevarskaya, N. Overexpression of an alpha 1H (Cav3.2) T-type calcium channel during neuroendocrine differentiation of human prostate cancer cells. *J. Biol. Chem. 2002*, *277*, 10824–10833. [CrossRef]
111. Taylor, J.T.; Huang, L.; Pottle, J.E.; Liu, K.; Yang, Y.; Zeng, X.; Keyser, B.M.; Agrawal, K.C.; Hansen, J.B.; Li, M. Selective blockade of T-type Ca²⁺ channels suppresses human breast cancer cell proliferation. *Cancer Lett. 2008*, *267*, 116–124. [CrossRef] [PubMed]
112. Barceló, C.; Sisó, P.; Maiques, O.; de la Rosa, I.; Martí, R.M.; Maciá, A. T-Type Calcium Channels: A Potential Novel Target in Melanoma. *Cancers 2020*, *12*, 391. [CrossRef] [PubMed]
113. Li, R.F.; Man, Q.W.; Liu, J.Y.; Zheng, Y.Y.; Gao, X.; Liu, H.M. Overexpression of T-type calcium channel Cav3.1 in oral squamous cell carcinoma: Association with proliferation and anti-apoptotic activity. *J. Mol. Histol. 2021*, *52*, 511–520. [CrossRef]
114. Mao, W.; Zhang, J.; Körner, H.; Jiang, Y.; Ying, S. The emerging role of voltage-gated sodium channels in tumor biology. *Front. Oncol. 2019*, *9*, 124. [CrossRef] [PubMed]
115. Litan, A.; Langhans, S.A. Cancer as a channelopathy: Ion channels and pumps in tumor development and progression. *Front. Cell. Neurosci. 2015*, *8*, 86. [CrossRef]
116. Leverrier-Penna, S.; Destaing, O.; Penna, A. Insights and perspectives on calcium channel functions in the cockpit of cancerous space invaders. *Cell Calcium 2020*, *90*, 102251. [CrossRef]
117. Visa, A.; Shaikh, S.; Alza, L.; Herreros, J.; Canti, C. The Hard-To-Close Window of T-Type Calcium Channels. *Trends Mol. Med. 2019*, *25*, 571–584. [CrossRef]
118. Yoshida, J.; Ishibashi, T.; Nishio, M. G1 cell cycle arrest by amlodipine, a dihydropyridine Ca²⁺ channel blocker, in human epidermoid carcinoma A431 cells. *Biochem. Pharmacol. 2007*, *73*, 943–953. [CrossRef]
119. Shaughnessy, M.; Lamuraglia, G.; Klebanov, N.; Ji, Z.; Rajadurai, A.; Kumar, R.; Flaherty, K.; Tsao, H. Selective uveal melanoma inhibition with calcium channel blockade. *Cardiovasc. Res. 2019*, *109*, 1090. [CrossRef]
120. Panneerpillai, P.; Yao, D.B.; Ganesan, K. Calcium channel blockers lercanidipine and amlodipine inhibit YY1/ERK/TGF-β mediated transcription and sensitize the gastric cancer cells to doxorubicin. *Toxicon. Vitr. 2021*, *74*, 105152. [CrossRef] [PubMed]
121. Principi, D.R.; Issa, A.F.; Kumar, S.; Pham, T.N.D.; Underwood, P.W.; Nair, R.; Ke, R.; Rana, B.; Trevino, J.G.; Munshi, H.G.; et al. Calcium channel blockers potentiate gemcitabine chemotherapy in pancreatic cancer. *Proc. Natl. Acad. Sci. USA 2022*, *119*, 18. [CrossRef] [PubMed]
122. Alandağ, C.; Karaman, E.; Yüce, E. Amlodipine improves the outcomes of regorafenib in metastatic colorectal cancer. *Anticancer. Drugs 2022*, *33*, 389–393. [CrossRef]
123. Taghizadehghelejoughi, A.; Sezen, S.; Hacimutfuoglu, A.; Güllüce, M. Vincristine combination with Ca²⁺ channel blocker increase antitumor effects. *Mol. Biol. Rep. 2019*, *46*, 2523–2528. [CrossRef]
124. El-Wakil, M.M.; Teleb, M.; Abu-Serie, M.M.; Huang, S.; Zamponi, G.W.; Fahney, H. Structural optimization, synthesis and in vitro synergistic anticancer activities of combinations of new N3-substituted dihydropyrimidine calcium channel blockers with cisplatin and etoposide. *Bioorg. Chem. 2021*, *115*, 105262. [CrossRef] [PubMed]
125. Sallan, M.C.; Visa, A.; Shaikh, S.; Nager, M.; Herreros, J.; Canti, C. T-type Ca²⁺ Channels: T for targetable. *Cancer Res. 2018*, *78*, 603–609. [CrossRef] [PubMed]
126. Rim, H.K.; Lee, H.W.; Choi, I.S.; Park, J.Y.; Choi, H.W.; Choi, J.H.; Cho, Y.W.; Lee, J.Y.; Lee, K.T. T-type Ca²⁺ channel blocker, KYS05047 induces G1 phase cell cycle arrest by decreasing intracellular Ca²⁺ levels in human lung adenocarcinoma A549 cells. *Bioorg. Med. Chem. Lett. 2012*, *22*, 7123–7126. [CrossRef] [PubMed]
127. Garrido-Laguna, I.; Tan, A.; Villarroel, M.; Rajeshkumar, N.; Rubio-Viqueira, B.; Gray, L.; Hidalgo, M. Activity of the T-type calcium channel antagonist Mibefradil in pancreatic cancer xenografts. In Proceedings of the Third AACR International Conference on Molecular Diagnostics in Cancer Therapeutic Development, Philadelphia, PA, USA, 22–25 September 2008.
128. Dziegielewiska, B.; Casarez, E.V.; Yang, W.Z.; Gray, L.S.; Dziegielewski, J.; Slack-Davis, J.K. T-type Ca²⁺ channel inhibition sensitizes ovarian cancer to carboplatin. *Mol. Cancer Ther. 2016*, *15*, 460–470. [CrossRef]
129. Pottle, J.; Sun, C.; Gray, L.; Li, M.; Pottle, J.; Sun, C.; Gray, L.; Li, M. Exploiting MCF-7 Cells’ Calcium Dependence with Interlaced Therapy. *J. Cancer Ther. 2013*, *4*, 32–40. [CrossRef]
130. Holdhoff, M.; Ye, X.; Supko, J.G.; Nabors, L.B.; Desai, A.S.; Walbert, T.; Lesser, G.J.; Read, W.L.; Lieberman, F.S.; Lodge, M.A.; et al. Timed sequential therapy of the selective T-type calcium channel blocker mibebradil and temozolomide in patients with recurrent high-grade gliomas. *Neuro-Oncology 2017*, *19*, 845–852. [CrossRef]
131. Kim, K.H.; Kim, D.; Park, J.Y.; Jung, H.J.; Cho, Y.H.; Kim, H.K.; Han, J.; Choi, K.Y.; Kwon, H.J. NNC 55-0396, a T-type Ca²⁺ channel inhibitor, inhibits angiogenesis via suppression of hypoxia-inducible factor-1α signal transduction. *J. Mol. Med. 2015*, *93*, 499–509. [CrossRef] [PubMed]
132. Tuan, N.M.; Lee, C.H. Penfluoridol as a Candidate of Drug Repurposing for Anticancer Agent. *Molecules 2019*, *24*, 3659. [CrossRef]
134. Mishra, S.K.; Hermosmeyer, K. Selective inhibition of T-type Ca\(^{2+}\) channels by Ro 40-5967. *Circ. Res.* 1994, 75, 144–148. [CrossRef] [PubMed]

135. Sedeeq, M.; Maklad, A.; Dutta, T.; Feng, Z.; Wilson, R.; Gueven, N.; Azimi, I. T-Type Calcium Channel Inhibitors Induce Apoptosis in Medulloblastoma Cells Associated with Altered Metabolic Activity. *Mol. Neurobiol.* 2022, 59, 2932. [CrossRef] [PubMed]

136. Alza, L.; Visa, A.; Herreros, J.; Canti, C. The rise of T-type channels in melanoma progression and chemotherapeutic resistance. *Biochim. Biophys. Acta-Rev. Cancer* 2020, 1873, 188564. [CrossRef] [PubMed]

137. Drolet, B.; Rousseau, G.; Daleau, P.; Cardinal, R.; Simard, C.; Turgeon, J. Pimozide (Orap) prolongs cardiac repolarization by blocking the rapid component of the delayed rectifier potassium current in native cardiac myocytes. *J. Cardiovasc. Pharmacol. Ther.* 2001, 6, 255–260. [CrossRef] [PubMed]

138. Tytgat, J.; Vereecke, J.; Carmeliet, E. Mechanism of L- and T-type Ca\(^{2+}\) channel blockade by flunarizine in ventricular myocytes of the guinea-pig. *Eur. J. Pharmacol.* 1996, 296, 189–197. [CrossRef]

139. Depuydt, A.S.; Rihon, J.; Cheneval, O.; Vanneert, M.; Schroeder, C.I.; Craik, D.J.; Lescrinier, E.; Peigneur, S.; Tytgat, J. Cyclic Peptides as T-Type Calcium Channel Blockers: Characterization and Molecular Mapping of the Binding Site. *ACS Pharmacol. Transl. Sci.* 2021, 4, 1379–1389. [CrossRef]

140. Kumari, N.; Giri, P.S.; Rath, S.N. Adjuvant role of a T-type calcium channel blocker, TTA-A2, in lung cancer treatment with paclitaxel. *Cancer Drug Resist.* 2021, 4, 996. [CrossRef]

141. Bhargava, A.; Saha, S. T-Type voltage gated calcium channels: A target in breast cancer? *Breast Cancer Res. Treat.* 2019, 173, 11–21. [CrossRef]

142. Meregalli, C.; Maricich, Y.; Cavaletti, G.; Canta, A.; Carozzi, V.A.; Chiorazzi, A.; Newbold, E.; Marmioli, P.; Ceresa, C.; Diani, A.; et al. Reversal of bortezomib-induced neurotoxicity by suvecaltamide, a selective T-type ca-channel modulator, in preclinical models. *Cancers* 2021, 13, 5013. [CrossRef] [PubMed]

143. Alza, L.; Visa, A.; Herreros, J.; Canti, C. T-type channels in cancer cells: Driving in reverse. *Cell Calcium* 2022, 105, 102610. [CrossRef] [PubMed]