Article

EDEn–Electroceutical Design Environment: Ion Channel Tissue Expression Database with Small Molecule Modulators

EDEn platform

Cassandra D.M. Churchill, Philip Winter, Jack A. Tuszynski, Michael Levin

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HIGHLIGHTS

Design of electroceuticals requires knowledge of ion channel targets and relevant drugs

EDEn allows rapid determination of which ion channels are expressed in a given tissue

EDEn also reveals what channel openers and blockers exist for any of the targets

This platform is a key enabling step for the design of bioelectric interventions
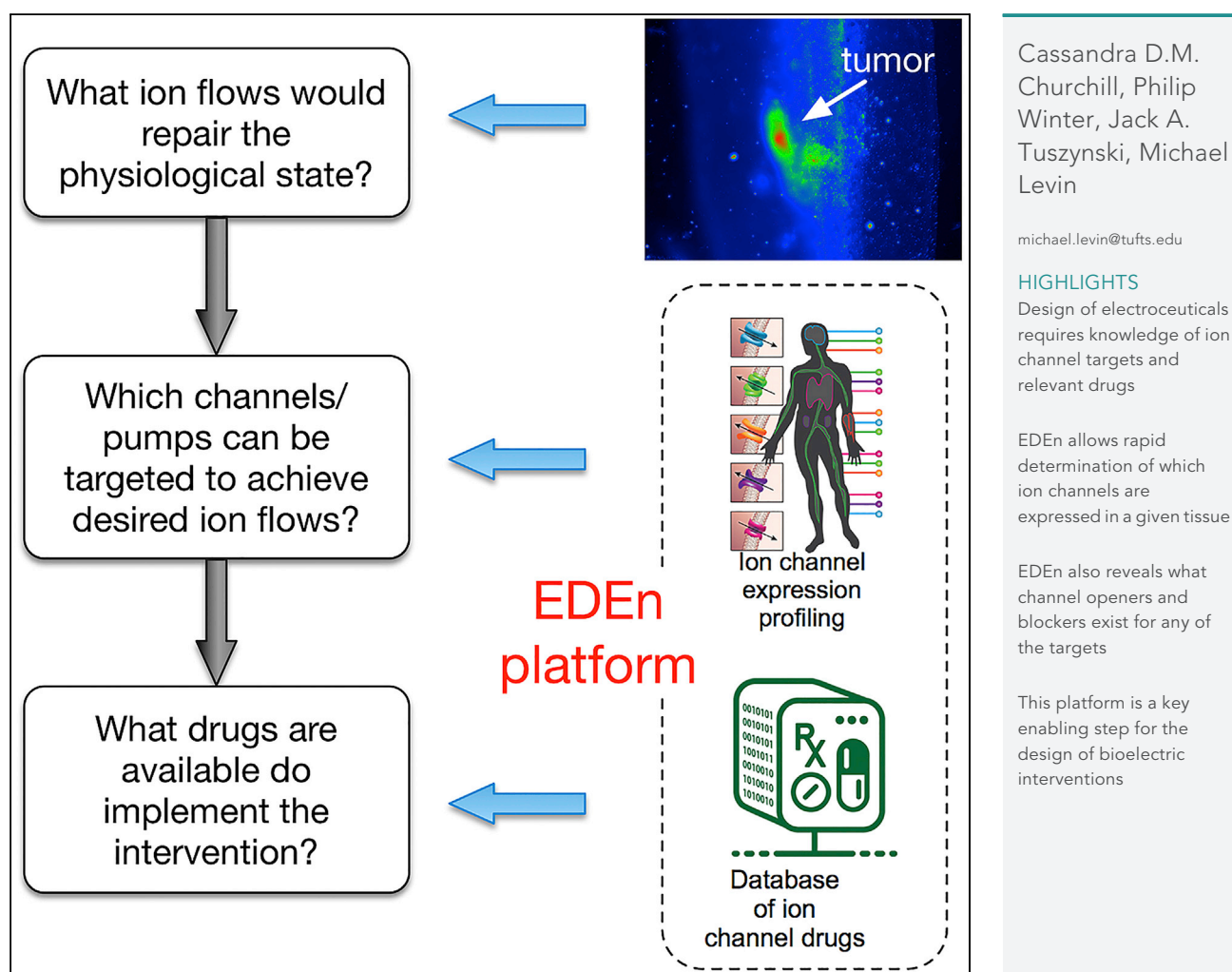
Article

EDEn–Electroceutical Design Environment: Ion Channel Tissue Expression Database with Small Molecule Modulators

Cassandra D.M. Churchill,[1] Philip Winter,[2] Jack A. Tuszynski,[1,2] and Michael Levin[3,4,*]

SUMMARY

The emerging field of bioelectricity has revealed numerous new roles for ion channels beyond the nervous system, which can be exploited for applications in regenerative medicine. Developing such biomedical interventions for birth defects, cancer, traumatic injury, and bioengineering first requires knowledge of ion channel targets expressed in tissues of interest. This information can then be used to select combinations of small molecule inhibitors and/or activators that manipulate the bioelectric state. Here, we provide an overview of electroceutical design environment (EDEn), the first bioinformatic platform that facilitates the design of such therapeutic strategies. This database includes information on ion channels and ion pumps, linked to known chemical modulators and their properties. The database also provides information about the expression levels of the ion channels in over 100 tissue types. The graphical interface allows the user to readily identify chemical entities that can alter the electrical properties of target cells and tissues.

INTRODUCTION

A major frontier in biomedicine and synthetic bioengineering is the development of computational and experimental tools for the rational design of interventions that drive desired changes in cell-, tissue-, and organ-level properties. Alongside well-known biochemical pathways, it is now known that bioelectric signaling driven by ion channel and pump proteins is a key determinant of growth, patterning, physiological maintenance, and repair (Funk, 2013; McLaughlin and Levin, 2018). The emerging field of molecular bioelectricity has revealed resting potential distributions across cell groups as a powerful instructive pathway for numerous events during embryogenesis, regenerative repair, and cancer suppression (Levin and Martyniuk, 2018; Levin et al., 2017; Mathews and Levin, 2018). Cell differentiation, proliferation, migration, and tissue morphogenesis receive inputs from bioelectric circuits outside the nervous system, and it is now clear that the bioelectric state is a tractable and powerful master regulator that can be exploited for control of tissue and organ patterning in numerous contexts (Levin, 2014; Pietak and Levin, 2018; McLaughlin and Levin, 2018; Bates, 2015). Recent work has revealed, for example, the control of human stem cell differentiation (Sundelacruz et al., 2008, 2009, 2013a, 2013b), immune system function (Li et al., 2016; Pare et al., 2017), tumor normalization (Chernet et al., 2014, 2016; Chernet and Levin, 2013a, 2013b, 2014), transplant innervation (Blackiston et al., 2015, 2017), and conversion of gut tissue into a functional eye (Pai et al., 2012) by specific modulation of bioelectric circuits that mediate signaling among cell networks (Levin et al., 2017; Pezzulo and Levin, 2015).

The possible modulation of these signals is increasingly becoming appreciated as a potential tool for regenerating tissue and curing disease including injury and cancer (Mobini et al., 2017; Leppik et al., 2015; Reid and Zhao, 2014; Feng et al., 2017; Cao et al., 2013; Zhao et al., 2012; Sanjuan-Alberte et al., 2018). For example, Kirson et al. reported the discovery that low-intensity (1–3 V/cm), intermediate-frequency (100–300 kHz) electric fields have a profoundly inhibitory effect on the growth rate of various mammalian tumor cell lines. This discovery has been translated into a clinical application termed "tumor-treating fields" for the treatment of glioblastoma multiforme (Kirson et al., 2004, 2007, 2009). Several ion channel drugs are also now being used to combat cancer (Fukushiro-Lopes et al., 2018; Lansu and Gentile, 2013; Checchetto et al., 2016; Kale et al., 2015). Numerous beneficial medical applications of electrical signals can be envisioned in the context of therapeutic use. However, a major challenge is to understand and guide the complexity of biophysical interactions induced by external field stimulation. Thus recent applications of bioelectricity to therapeutic contexts have focused on control of endogenous cellular ionic and voltage gradients by modulating ion channel function.

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Work in amphibian model systems (e.g., *Xenopus laevis*) has revealed that misexpression of carefully selected ion channels can repair brain defects due to teratogenic insult (Pai et al., 2018) or even mutation (Pai et al., 2015a, 2015b), reprogram and suppress oncogene-mediated tumorigenesis (Chernet et al., 2014, 2016; Chernet and Levin, 2013b, 2014), augment innate immune system function (Pare et al., 2017), expand neural connectivity and function of implanted tissues (Blackiston et al., 2015, 2017), and induce regeneration of whole appendages, including the spinal cord and muscles (Adams et al., 2007). Moreover, the existence of a plethora of pharmacological agents targeting ion channels allows small molecule approaches that achieve the desired bioelectric state change without the need for gene therapy using exogenous channel proteins. Successful examples include the induction of whole leg regeneration in *Xenopus* by an ionophore cocktail (Tseng et al., 2010), the use of ion channels in human tissues *in vitro* (Li et al., 2016; Ozkucur et al., 2015; Sundelacruz et al., 2008, 2013a; Thurber et al., 2017), and the increasing use of ion channel drugs as anti-cancer agents in mammals (Huang et al., 2012, 2015; Huang and Jan, 2014; Kokel et al., 2013; Klumpp et al., 2016; Brackenbury, 2012; Arcangeli et al., 2012; Schickling et al., 2011; Arcangeli and Becchetti, 2010).

The most attractive feature of bioelectric signaling is that it frequently serves as a master regulator that rapidly triggers very complex, highly coordinated downstream programs that do not have to be micromanaged (Pezzulo and Levin, 2015, 2016; Levin and Martyniuk, 2018; Herrera-Rincon et al., 2018). In addition to such applications in regulating growth and patterning, a plethora of applications in neurology, cardiology, and other aspects of pathophysiology await tools that enable efficient control of ionic signaling and bioelectric state within and across tissues.

Thus, we and others have proposed a roadmap (Figure 1) of using predictive modeling platforms (Cervera et al., 2014, 2016a, 2016b, 2017, 2018a, 2018b; Garcia-Morales et al., 2017; Pietak and Levin, 2016, 2017, 2018; Pai et al., 2018; Levin et al., 2018) for the development of rational control of patterning in biomedical contexts by ion channel modulators or "electroceuticals." Specifically, given the knowledge of the bioelectric state corresponding to the desired (healthy) form and function of a given tissue, one can use predictive physiological simulators (Cervera et al., 2018b; Pietak and Levin, 2016) to determine which ion channels should be opened or closed to reprogram the bioelectric circuit from its current (diseased or immature) state into a desired state, with the concomitant downstream changes in transcriptional and epigenetic profile. One benefit is that many ion-channel-modulating pharmacological agents are already approved by the United States Food and Drug Administration (FDA) for human use in arrhythmias, epilepsy, and other conditions (Bagal et al., 2013; Kaczorowski et al., 2008; McGivern, 2007; Yogeeswari et al., 2004) and thus can be repurposed for bioelectrical control in regenerative medicine and other applications. In addition to developing technology for localized delivery (Sanjay et al., 2018; Mancera-Andrade et al., 2018; Damiati et al., 2018), the needed effects can also be achieved with systemic delivery: effects can be largely focused on one tissue by taking advantage of unique channels or pumps that are only expressed in that cell type(s) (Tseng et al., 2010; Blackiston et al., 2011; Lobikin et al., 2015b).

Equally important is the identification of channels that could protect other tissues in a proposed electroceutical strategy (e.g., what combination of drugs will hyperpolarize nascent metastatic cells without affecting heartbeat in cardiac tissue). However, a major barrier to the broad use of these strategies is the lack of computational tools for rapidly ascertaining relevant targets in a tissue of interest and identifying existing small molecule compounds that could modulate the electrogenic proteins in those cells in the ways needed to achieve a desired bioelectric state. To design an electroceutical strategy, one first needs to know which channels and pumps are present in which tissue and what reagents exist to modulate them specifically. This is an essential first-step information that needs to be fed into a predictive computational model (Cervera et al., 2018b; Pietak and Levin, 2016, 2017, 2018; Pai et al., 2018; Levin et al., 2018). The proliferation of computational tools and databases designed to assist with genomic and biochemical approaches has not yet been extended to assist scientists with designing bioelectrical and physiological interventions.

Here we report the first platform front-end designed to accelerate the design of electroceuticals and their blends. The electroceutical design environment (EDEn) ion channel database and web server is a tool that researchers can use to obtain information about ion channels expressed in a specific tissue or cell type (both healthy and in a range of disease states). Having thus obtained a list of potential ion
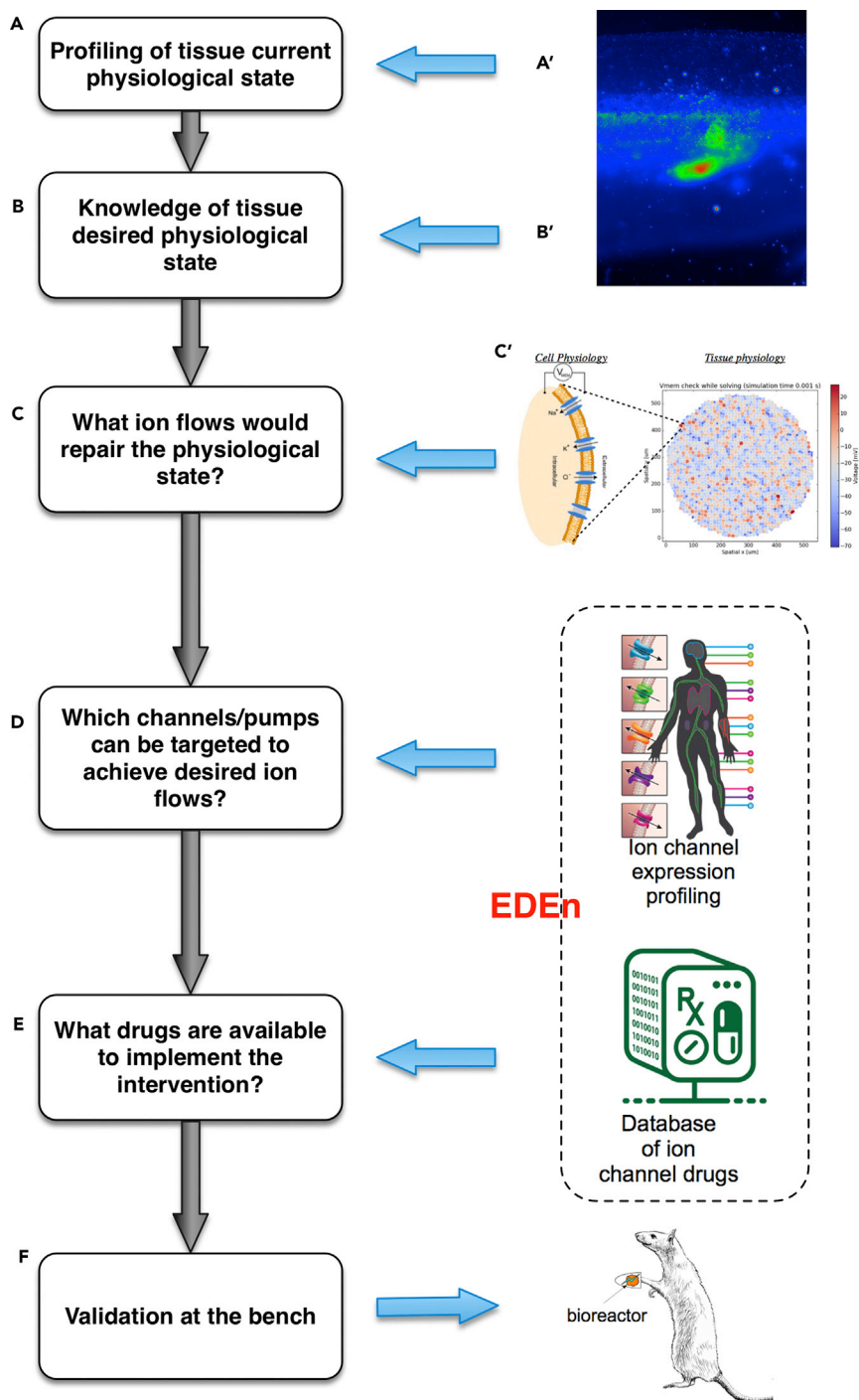
Figure 1. Schematic of Approach for Design of Electroceuticals in Regenerative Medicine

(A) First, the current bioelectric state of the tissue is ascertained using techniques like voltage reporter fluorescent dyes (A′) or traditional electrophysiology. This is compared with the correct (healthy) state of the same tissue (B, B′); to determine what ion flows would convert the current (disease) state to the healthy bioelectric state (C), computational models (physiological simulators, C′) are used. The EDEn system facilitates the subsequent steps: identify specific ion channels and pumps that, if modulated, would implement the needed change in ion currents (D), and determine drugs that target those electrogenic proteins in the desired way (E). The predicted small molecule blends are then tested (F) to validate the strategy before biomedical deployment.
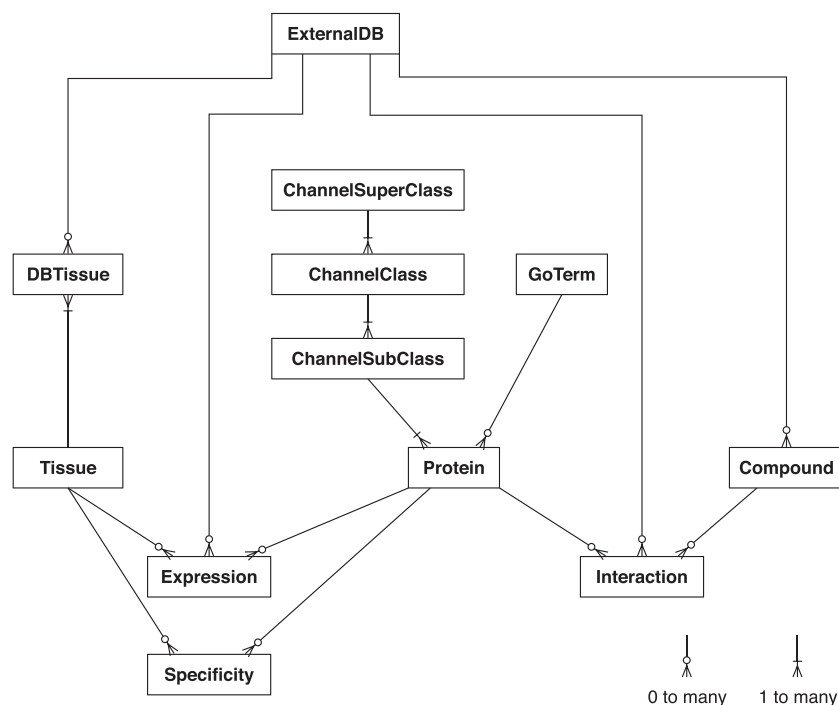
Figure 2. Schema of the EDEn Database

Tables are shown as rectangular boxes. Relations between tables are shown as lines. Multiplicity of table relationships is shown using Crow's Foot notation.

channel and pump targets, the user can then rapidly identify a list of available pharmacological agents (ideally FDA-approved drugs) for their modulation. This method enables selection of channels with desired tissue specificity and availability of blockers/activators with desired properties. This information can then be fed into existing simulators (Pietak and Levin, 2016, 2017); currently, such iterative search must be performed manually, which greatly delays the process and is prone to human error. The EDEn database works together with the web server providing a graphical front end that can be used to access information contained in the database. The database integrates data from multiple public data sources, and updated data can be added to the database in an automated fashion as new profiling, genomic, and drug data are reported. This platform can be used for biomedical purposes, as well as to identify reagents for control of cell behavior in bioengineering, synthetic biology, and numerous other contexts *in vitro* and *in vivo*. Thus this versatile tool significantly lowers the entry barrier for workers in basic and applied physiology, seeking to identify targets and reagents for pilot experiments or large focused studies.

RESULTS

Database Schema

The database is a relational database. The database schema is illustrated in Figure 2. The core of the database is data centered on human tissue types and human ion channels. This data are stored in two tables, the Tissue table and the Protein table.

The Tissue table (Figure 3) contains data about a variety of human tissue and cell types, both referred to as tissues in the platform. The tissues that were selected for inclusion in the platform were those for which expression data were available. The names of the tissues are based on the Brenda Tissue Ontology (www.brenda-enzymes.org/ontology.php?ontology_id=3) (Gremse et al., 2011). The Tissue table includes both healthy tissue types and cancer tissue types. The database supports hierarchical relationships between tissues (for example, the brain is a part of the central nervous system); however, this information is currently not used by the web front end. A supporting table, DBTissue, is used to associate the tissue names used by the platform with the names or IDs used by the data sources.
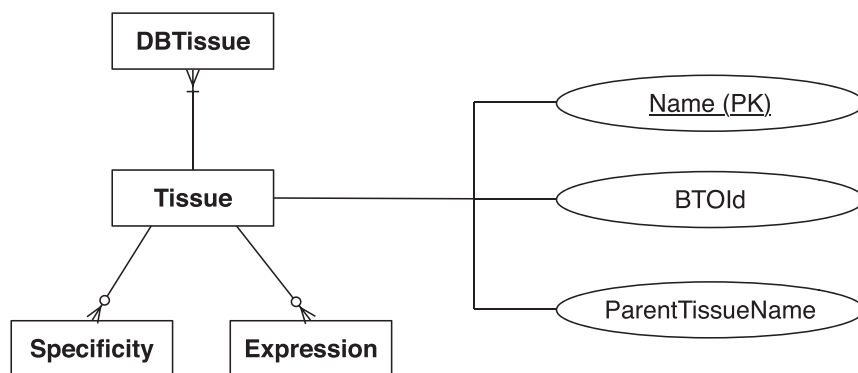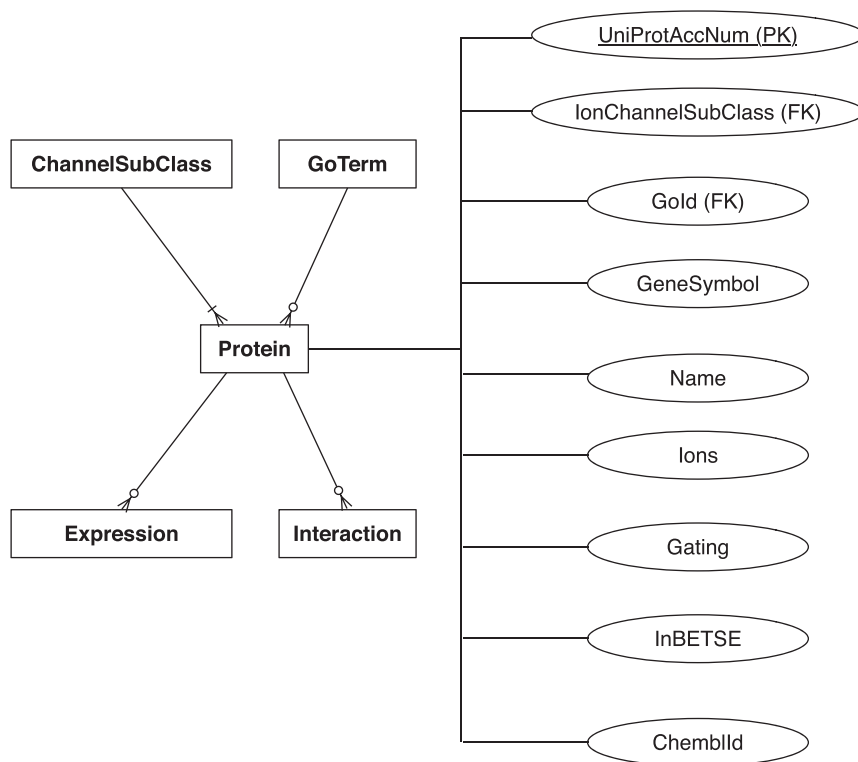
Figure 3. Tissue Table

A schematic representation of the tissue table in the EDEn database. Tables are shown as rectangular boxes. Fields are shown as ovals. Primary keys are underlined and marked with (PK). Multiplicity of table relationships is shown using Crow's Foot notation.

The Protein table (Figure 4) contains data about human ion channel proteins and the corresponding genes. The ion channel data is protein centric, with the UniProt accession number used as the primary key for Protein table. The table includes information important for the platform, including a Boolean field that records if the ion channel has parameters for simulation in BETSE (BioElectric Tissue Simulation Engine; Pietak and Levin, 2016). One limitation of the current data model is that information about ion channels that consist of a complex of proteins is not handled. Two supporting tables, ChannelSubClass (see below) and GoTerm, are used to store classification information about the ion channels. The GoTerm table has relevant terms from the Gene Ontology database (Ashburner et al., 2000).

The Expression table (Figure 5) associates a record in the Tissue table with a record in the Protein table. The table contains information about the abundance of each ion channel in each tissue. The intent of this information is that it can be used to identify ion channel targets for a particular tissue known to the user. The table supports both quantitative expression information and categorical expression information. The categorical expression data have four expression levels: high, medium, low, and not detected. The database design supports multiple expression records for each Tissue-Protein pair. If multiple records exist, then the web interface prefers to use quantitative data when available. One limitation of the current approach is that combining expression data from multiple sources is not currently possible. The supporting table ExternalDB is used to store information about the data source for the expression data.

The Specificity table (Figure 6) is based on the expression data. This table contains a specificity score for each Tissue-Protein pair in the database that has quantitative expression data. The score is a calculated value wherein higher numbers correspond to ion channels that tend to be highly expressed only in the associated tissue and not in many other tissues and lower numbers correspond to ion channels that have high expression in many tissues, that is, those that are ubiquitously expressed.

The Compound table (Figure 7) contains data about each compound (including approved or investigational drugs). Each compound is classified as either a "compound" or a "drug" based on its categorization in the ChEMBL database. The Name field of the table is the primary name of the compound; in the case of the drug, this is the drug common name, and in the case of other compounds, this is generally an International Union of Pure and Applied Chemistry (IUPAC) name. The Synonym field of the table is a list of zero or more alternate names for the compound, for example, a trade name of a drug or an IUPAC name. A future version of the database is planned to include additional information about each compound, including a chemical structure in SMILES or InChI format, and allow the user to view the chemical structure in the web interface. The ExternalDB table is used to link the Compound table with the data source for the compound; in the current version of the database this is always ChEMBL. It should be mentioned that for practical applications such as *in vitro* assays involving some of the compounds found in this database, additional information about their properties needs to be acquired from additional resources available both publicly (e.g., https://www.drugbank.ca) or commercially (e.g., ADMET Predictor from
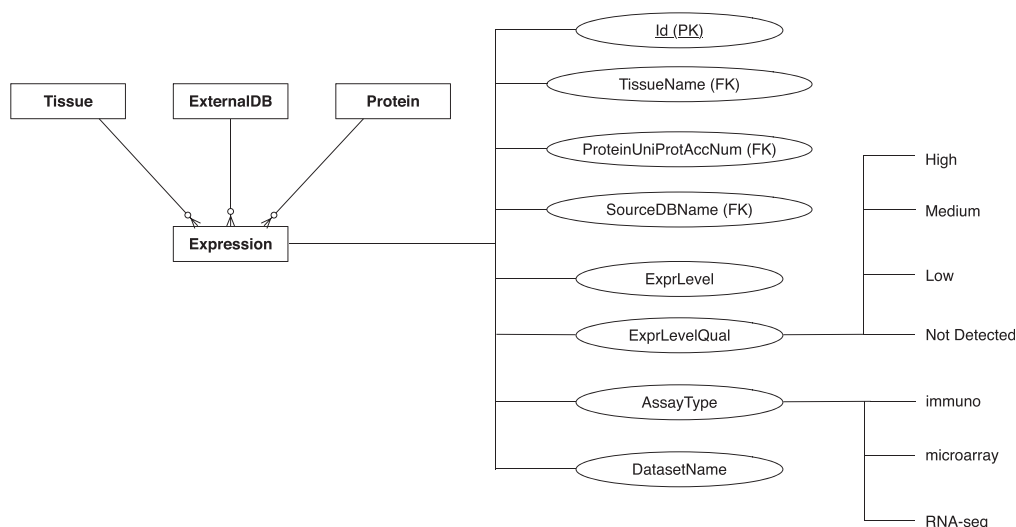
Figure 4. Protein Table
A schematic representation of the protein table in the EDEn database. Tables are shown as rectangular boxes. Fields are shown as ovals. Primary keys are underlined and marked with (PK). Foreign keys are marked with (FK). Multiplicity of table relationships is shown using Crow's Foot notation.

https://www.simulations-plus.com/software/admetpredictor/). These resources can inform the interested user regarding both the pharmacokinetic and pharmacodynamic properties of the compounds in question, some of which may be FDA-approved drugs. For example, the log p values, the solubility value, the blood-brain barrier permeability coefficient, or the diffusion coefficient can all be estimated using *in silico* prediction, or in some cases found from experimental data sources.

The Interaction table (Figure 8) contains data about the interaction of a Protein-Compound pair. The ActionType field includes information about the type of interaction (e.g., blocker, activator, modulator). The intent of this table is that once the user has identified an ion channel target (or targets), he or she will then use the platform to search for compounds that have an effect on the target. The strength of the interaction is stored in the AssayValue field, which is a parameter calculated from an appropriate assay of the compound with the protein. The assay values are generally IC_{50} values, but they may also include EC_{50}, K_i, or K_d values. A limitation of the current approach is that specificity information about compounds for ion channel targets is not used by the platform, that is, the platform can be used to identify compounds that are potent against a given target, but the identified compound may also be potent against other ion channels that the user does not intend to target. The information in this table is based on assay data from the ChEMBL database.

Last, the ChannelSuperClass, ChannelClass, and ChannelSubClass tables (see Figure 9) are used to store hierarchical information about a hierarchical classification of ion channels. For example, SuperClass = K (potassium), Class = Kv1, and SubClass = Kv1.1. The six superclasses are chloride, potassium, sodium, calcium, proton channels, and non-selective cation channels. The 27 classes and 169 subclasses can be found in channelpedia.epfl.ch.

The number of records in each table is given in Table 1.

Figure 5. Expression table
A schematic representation of the expression table in the EDEn database. Tables are shown as rectangular boxes. Fields are shown as ovals. Primary keys are underlined and marked with (PK). Foreign keys are marked with (FK). Possible values for some fields are also shown. Multiplicity of table relationships is shown using Crow's Foot notation.

Web Server

The web server provides a graphical user interface to the ion channel database. Figure 10 is a screenshot of the web interface. Figure 11 shows a typical screenshot of the results. The main use case supported by the web interface is described in the text that follows:

1. The user selects one or more tissues.

2. The user selects an expression threshold. Only ion channels with expression greater than or equal to the threshold will be shown. This option only works when quantitative expression data are available. In addition, the user may select the option "Include BETSE ion channels?". If this option is selected, all ion channels that are supported in BETSE will be shown, ignoring the expression threshold for those ion channels. This feature is included as part of integration with the most comprehensive modeling package (BETSE).

3. Select Comprehensive to show all channels expressed in the selected tissues (ordered by the most specific first). Select Unique to show only channels that are specific to the selected tissues. (This feature will be implemented in the future.)

4. Select one or more ion channels. Info about the selected ion channel from Channelpedia will be shown in the panel on the right, if available.

5. Click Lookup. The requested data will be retrieved from the database and displayed in a table to the user.

The web server and database are running on an Amazon Web Services instance. The operating system is Ubuntu 16.04 LTS Linux. The web server was built using the Django web framework. Django is a Python-based web framework. The Apache HTTP server is also used as part of the web stack. The Django web code interfaces with the Python database access routines. The web server also uses JavaScript, jQuery, and Ajax to update the page without reloading. The source code is maintained in a public GitHub repository. The web server is free to access.

DISCUSSION

Design of next-generation biomedical interventions, especially those with the advantage of not involving gene therapy, will require a tight integration of genetic, biochemical, and physiological data. We present a contribution to the developing fields of bioelectricity and functional bioinformatics, which facilitate the
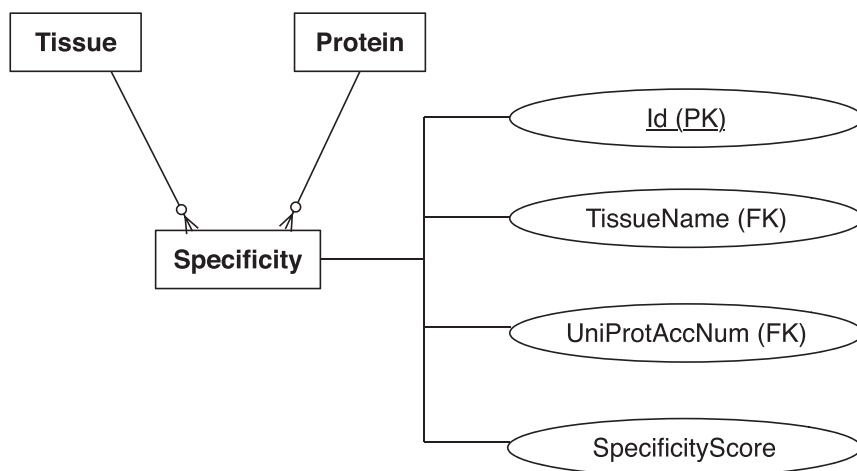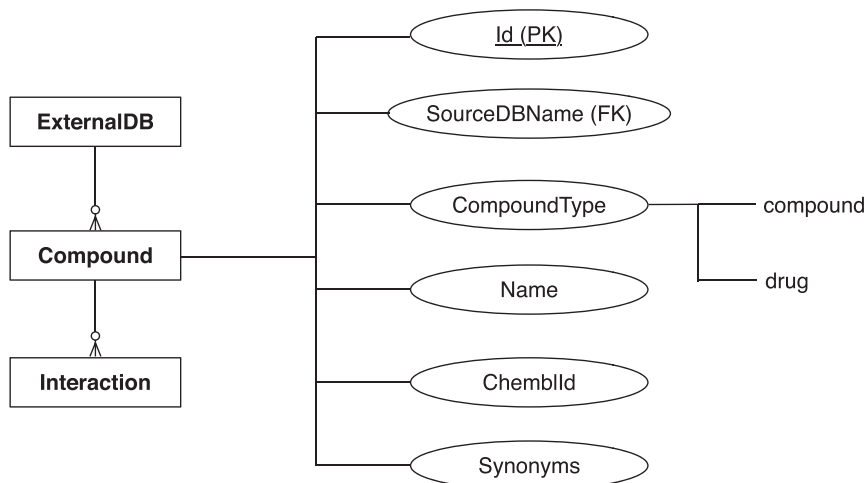
Figure 6. Specificity Table

A schematic representation of the specificity table in the EDEn database. Tables are shown as rectangular boxes. Fields are shown as ovals. Primary keys are underlined and marked with (PK). Foreign keys are marked with (FK). Multiplicity of table relationships is shown using Crow's Foot notation.

discovery of strategies to manage system-wide physiological signaling. Existing examples of this approach are the repolarization of KRAS mutation-induced tumors (normally depolarized), which results in the prevention or normalization of tumorigenesis (Chernet et al., 2014, 2016; Chernet and Levin, 2013a, 2013b, 2014; Lobikin et al., 2012), and the forced bioelectric prepattern (induced by activating HCN2 channel function), which results in normal embryonic brain development despite the presence of mutations and chemical teratogens, which reduce the resting potential difference between nascent brain cells and nearby tissues (Pai et al., 2015a, 2015b, 2018).

Understanding the real-time dynamics of bioelectric signals in a tissue is extraordinarily complex given the voltage sensitivity of ion channels and gap junctions and the intricacy of the resulting feedback loops. To address the need for a biorealistic model, members of our team have previously developed the BETSE (Pietak and Levin, 2016), which has already led to the successful discovery of agents that

Figure 7. Compound Table

A schematic representation of the chemical compound table in the EDEn database. Tables are shown as rectangular boxes. Fields are shown as ovals. Primary keys are underlined and marked with (PK). Foreign keys are marked with (FK). Possible values for some fields are also shown. Multiplicity of table relationships is shown using Crow's Foot notation.
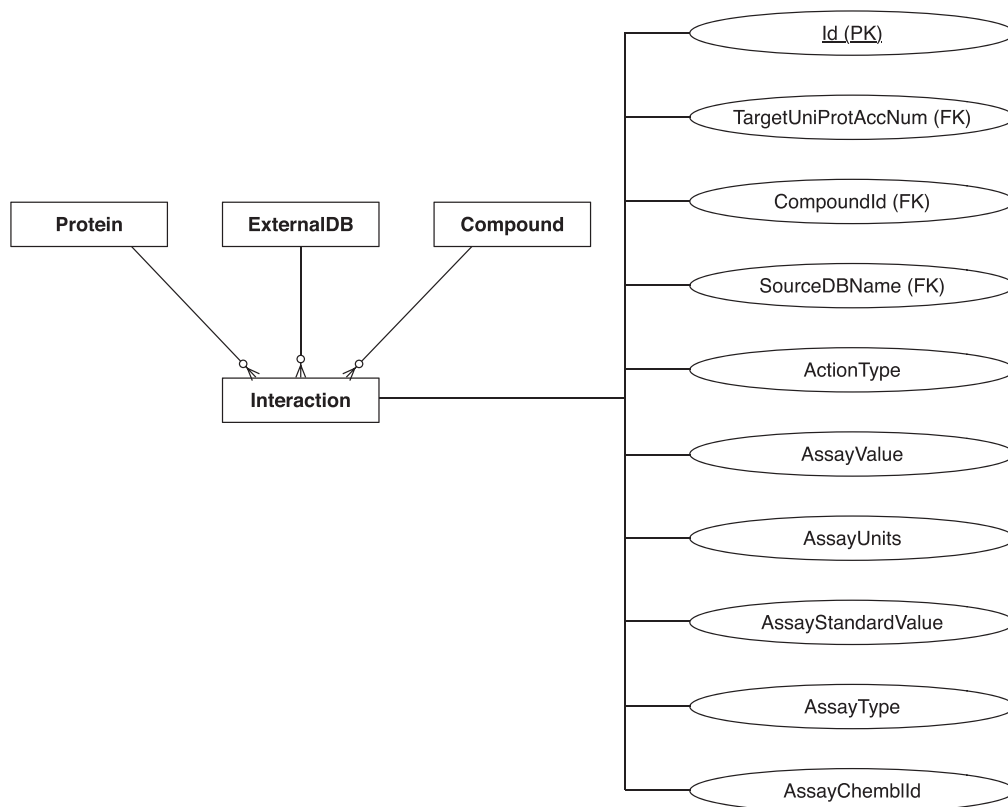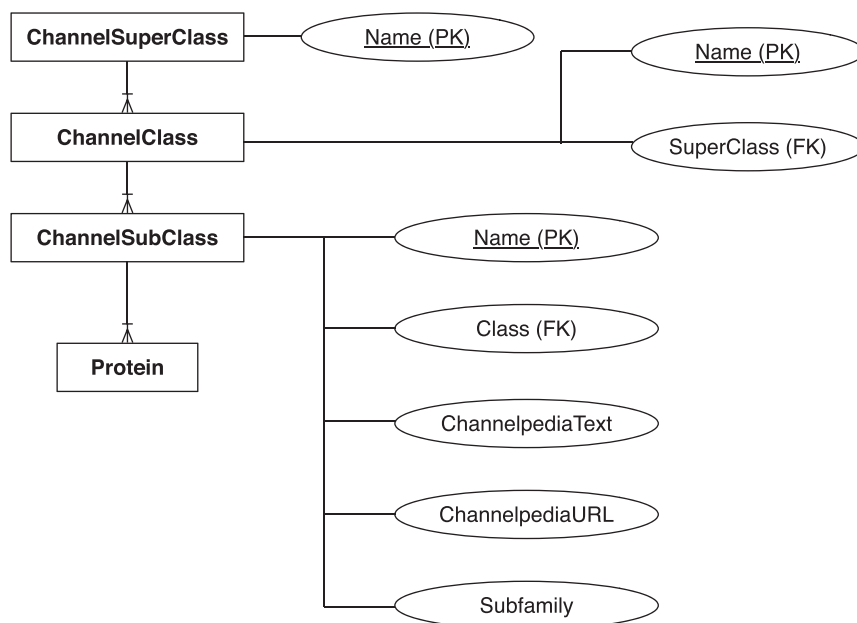
Figure 8. Interaction Table

A schematic representation of the protein-drug interaction table in the EDEn database. Tables are shown as rectangular boxes. Fields are shown as ovals. Primary keys are underlined and marked with (PK). Foreign keys are marked with (FK). Multiplicity of table relationships is shown using Crow's Foot notation.

repair brain morphology and function despite a range of diverse teratogenic insults (Pai et al., 2018). Such tools model ion channel and gap junction activity to predict bioelectric patterns across tissues, and the resulting changes to membrane potential upon modulation of channels. As inputs to the strategy of using these models to design interventions targeting specific body tissues and organs, knowledge of tissue-specific channel expression and availability of relevant functional small molecules is required. The EDEn database is an essential input to pipelines that use simulators and other strategies to design pharmacological interventions, to enable the modeling components to know which native electrogenic components to model and which can be targeted. Our database allows users to rapidly (1) determine the expression of ion channels in target tissues, thus acquiring a (ranked) list of potential targets for manipulation *in vivo* and (2) identify existing compounds known to modulate a given channel, and their specific effect on that channel (a required step for implementing the designed strategies).

In its current stage (v1.0), it is an essential tool for human users creating physiological models of specific organs/tissues in health and disease, and designing interventions based on those models. However, another use case for this system is as part of an artificial intelligence tool, in which automated approaches (Sparkes et al., 2010; Qi et al., 2010; King et al., 2009) use this information to help design interventions. Subsequent development will automate the integration of the EDEn system with machine-learning-based model discovery platforms (Lobo et al., 2013a, 2013b, 2014a, 2014b, 2016a, 2016b, 2017; Lobo and Levin, 2015; Lobikin et al., 2015a), to enable high-efficiency automated discovery of candidate drug blends in a broad range of biomedical scenarios.

Future versions of EDEn will also add significant new functionality, besides being continuously updated with the latest information in the growing channel expression and drug databases. First, the growing

Figure 9. Channel Class Tables

A schematic representation of the channel class tables in the EDEn database. Tables are shown as rectangular boxes. Fields are shown as ovals. Primary keys are underlined and marked with (PK). Foreign keys are marked with (FK). Multiplicity of table relationships is shown using Crow's Foot notation.

number of cell resolution profiling efforts will enable distinct information on single-cell profiles versus complex tissue and organ contexts (for example, the expression database contains mRNA data from single cell types as well as from heterogeneous tumors). Second, increasing data on structure-function relationships in ion channels and pumps will allow inclusion of data on drug effects on mutated channels, and on non-ion-passing functions of channel proteins (which can easily be accommodated by including such signaling in the simulation steps). Third, the database will be extended to powerful model species such as mouse, *Xenopus*, zebrafish, etc. Finally, we will be including forthcoming proteomic and physiomic datasets, to improve accuracy given the fact that mRNA expression data are only an estimate of the eventual bioelectric state of the cell (given the many steps involved, such as differential splicing, translation, membrane targeting, and gating).

Table	No. of Records
Tissue	120
Protein	747
Compound	33,483
Expression	79,830
Specificity	35,475
Interaction	103,048
GoTerm	2,177
ChannelSuperClass	6
ChannelClass	27
ChannelSubClass	169

Table 1. Total Number of Records in the Main Database Tables

A detailed description of each table is found in the database schema section.

EDEn - Electroceutical Design Environment

A tissue specific ion channel database

1. Select one or more tissues:

Normal tissues:

- bronchus
- temporal lobe
- testis
- thalamus
- thymus
- thyroid gland
- tongue
- tonsil
- trachea
- urinary bladder
- uterine cervix
- uterine endometrium
- uterus
- nasal nerve
- adipose tissue

Cancer tissues:

- colorectal adenocarcinoma cell
- breast cancer cell
- cervical carcinoma cell
- thyroid cancer cell
- testicular cancer cell
- gastric cancer cell
- glioma cell
- lung cancer cell
- pancreatic cancer cell
- liver cancer cell
- uterine adenocarcinoma cell
- K-562 cell
- kidney cancer cell
- carcinoid cell
- HL-60 cell

2. Show ion channels with mRNA expression level greater than [10] ☐ Include BETSE ion channels?

3. Select comprehensive to show all channels expressed in the selected tissues (ordered by most specific first).
Select Unique to show only channels that are specific to the selected tissues.

- ⦿ Comprehensive
- ◯ Unique

4. Select one or more ion channels:

- ATP-sensitive inward rectifier potassium channel 15 (Q99712|KCNJ15)
- Annexin A6 (P08133|ANXA6)
- Anoctamin-6 (Q4KMQ2|ANO6)
- Apolipoprotein L1 (O14791|APOL1)
- Aquaporin-1 (P29972|AQP1)
- Aspartyl/asparaginyl beta-hydroxylase (Q12797|ASPH)
- CaM kinase II (Q13557|CAMK2D)
- Calcium homeostasis modulator protein 2 (Q9HA72|CALHM2)
- Calcium uptake protein 1, mitochondrial (Q9BPX6|MICU1)
- Calcium uptake protein 2, mitochondrial (Q8IYU8|MICU2)
- Calcium-activated potassium channel subunit alpha-1 (Q12791|KCNMA1)
- Calsequestrin-2 (O14958|CASQ2)
- Chloride channel CLIC-like protein 1 (Q96S66|CLCC1)
- Chloride intracellular channel protein 1 (O00299|CLIC1)
- Chloride intracellular channel protein 2 (O15247|CLIC2)

[Lookup]

Figure 10. A Representative Screenshot of the Web Interface

One of the major questions for applications of bioelectrics to medicine is "how can we apply bioelectric manipulations in the patient, without using transgenics to introduce new ion channels as gene therapy, in patients"? A powerful set of strategies is to use rationally designed combinations of ion channel drugs to open and close specific endogenous ion channels to produce bioelectrical distributions that drive desirable downstream cell behaviors. Remarkably, such approaches have already been used to repair even genetic defects such as mutant NOTCH and KRAS proteins (Chernet et al., 2014, 2016; Chernet and Levin, 2013b, 2014; Pai et al., 2015b). How can we determine which drugs to use? The answer requires at least two components: (1) knowing which channels are present in the target tissue (and how to use that information to avoid untoward side effects in other organs) and (2) inferring what pattern of channel opening and closing must be achieved to make the necessary bioelectric state happen. The goal of this research was to create a software system to assist with the development of such strategies. This platform will suggest (a combination of) channel drugs that preferentially targets the tissue in question and sets up the desired bioelectric state, capitalizing on differences in channel expression and availability of lots of drugs with overlapping specificities. The EDEn database enables the execution of such a program. This will require an integration of EDEn with the physiological simulator BETSE. The ultimate goal is to turn the combination of products into a turnkey system for predicting drug cocktails, exploiting known drugs (many of which are already human approved) and the battery of compounds

Figure 11. A Typical Screenshot of the Results Generated by EDEn

sitting unused in drug companies, which "failed" unsophisticated tests (Maier et al., 2018; Juarez et al., 2018; Nelson et al., 2015; Koltai, 2015; Kale et al., 2015). This database makes such an approach possible (Levin, 2011).

Limitations of the Study

In this article, we report the first platform front-end designed to accelerate the design of electroceuticals. The EDEn ion channel database and web server is a tool that researchers can use to obtain information about ion channels expressed in a specific tissue or cell type (both healthy and in a range of disease states). This is a versatile tool that significantly lowers the entry barrier for workers in basic and applied physiology seeking to identify targets and reagents for pilot experiments or large focused studies. However, there are several limitations, which will be addressed by updating EDEn in the future. First, the current data model does not handle information about ion channels that consist of a complex of different proteins. Second, the ability to combine expression data from multiple sources is not currently implemented. Furthermore, specificity information about compounds for ion channel targets is not used by the platform; that is, the platform can be used to identify compounds that are potent against a given target, but the identified compound may also be potent against other ion channels that the user does not intend to target.

Data and Software Availability

The web server may be accessed at http://eden.pharmamatrix.ca. The source code for the database and web server are available at https://github.com/pwinter3/IonChannel.git and https://github.com/pwinter3/IonChannelWeb.git, respectively.

METHODS

All methods can be found in the accompanying Transparent Methods supplemental file.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Transparent Methods and can be found with this article online at https://doi.org/10.1016/j.isci.2018.12.003.

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AUTHOR CONTRIBUTIONS

M.L. conceived the project. J.A.T. and M.L. designed the method of approach. C.D.M.C. and P.W. worked on the database. P.W. worked on the web server. J.A.T. and M.L. supervised the project. All authors contributed to writing the paper.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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Supplemental Information

EDEn–Electroceutical Design Environment:

Ion Channel Tissue Expression Database

with Small Molecule Modulators

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Transparent Methods

Data Base Implementation

Human ion channel proteins were identified using gene ontologies (GO:0005216 "ion channel activity" and GO:0034702 "ion channel complex") extracted using the QuickGO browser (Binns et al., 2009), providing a total of 747 unique proteins (UniProt accession numbers) corresponding to 551 unique genes (gene symbols). These UniProt accession numbers were used to search the ChEMBL database (version 23) (Bento et al., 2014) for compounds, including approved drugs, known to interact with these protein targets and to extract assay information, at this point focused on IC_{50}, EC_{50}, K_a, and K_d values. For each compound identified, its charge at a physiological pH was calculated using the Schrodinger software (Borgens, 1988; Schrödinger, 2015). Information for the indicated assays was available for 747 proteins, resulting in 103,048 assay annotations for 33,483 unique drugs and chemical compounds in our database (as of December 14, 2017).

Data Sources

Below is the list of data sources used to create and populate the database.

1. ChEMBL includes assay data including targets, compounds, parameters measured, type of assay. Compound data including compound names and structures (Gaulton et al., 2017). www.ebi.ac.uk/chembl/
2. Brenda Tissue Ontology contains a vocabulary for human tissues and cell types. It includes synonyms for tissue names and tissue relationships. www.brenda-enzymes.org/ontology.php?ontology_id=3
3. UniProt lists protein and gene identifiers to link different data sources. www.uniprot.org
4. GeneOntology: Info about functions of genes and gene products (Ashburner et al., 2000). www.geneontology.org
5. Human Protein Atlas contains gene and protein expression data in human tissue samples (Uhlen et al., 2010) www.proteinatlas.org
6. BioGPS lists gene expression data in human tissue samples (Wu et al., 2009). biogps.org
7. Channelpedia contains massive information about classification of ion channels (Ranjan et al., 2011). Text descriptions of ion channels can be found at channelpedia.epfl.ch

Additional files included in EDEn contain information about ion channels available in BETSE (Pietak and Levin, 2016b) and the values of the electrostatic charges of the listed compounds that have been calculated by us, which will be included in a future version of the database. Generally, the procedure used in the creation of EDEn is that a copy of the database must be downloaded to the database server, then Python scripts are run to extract the required info from the database. In some cases, the Python script pulls the data directly from the data source's website.

To give an overview of the amount of information contained in EDEn we provide database statistics in Table 1. Database implementation details are given next. The ion channel database was implemented using Python and SQLite. Python code is used to parse data from the source databases and create the ion channel database. There are also Python routines to access information in the database. The Python code generates the required SQL statements and connects to the SQL database. All Python code is written for Python version 2.7. The SQLite version 3 database engine is used. The source code is available in a public GitHub repository.