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Bioelectrical approaches to cancer as a problem of the scaling of the cellular self

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ABSTRACT

One lens with which to understand the complex phenomenon of cancer is that of developmental biology. Cancer is the inevitable consequence of a breakdown of the communication that enables individual cells to join into computational networks that work towards large-scale, morphogenetic goals instead of more primitive, unicellular objectives. This perspective suggests that cancer may be a physiological disorder, not necessarily due to problems with the genetically-specified protein hardware. One aspect of morphogenetic coordination is bioelectric signaling, and indeed an abnormal bioelectric signature non-invasively reveals the site of incipient tumors in amphibian models. Functionally, a disruption of resting potential states triggers metastatic melanoma phenotypes in embryos with no genetic defects or carcinogen exposure. Conversely, optogenetic or molecular-biological modulation of bioelectric states can override powerful oncogenic mutations and prevent or normalize tumors. The bioelectrically-mediated information flows that harness cells toward body-level anatomical outcomes represent a very attractive and tractable endogenous control system, which is being targeted by emerging approaches to cancer.

1. Introduction

1.1. Multicellularity binds cells toward large-scale morphogenetic goals (Fig. 1)

(A) Fertilized eggs create embryonic cells which cooperate to invariably form complex 3-dimensional anatomies. (B) Remarkably, these target morphologies are not simply emergent outcomes of feed-forward processes: cell collectives in many species will undertake new activity to repair damaged bodies, and stop when the correct pattern is complete, such as the salamander limb regeneration schematized here (Birnbaum and Alvarado, 2008): the cells grow rapidly, but unlike a tumor, the whole process ceases when a proper limb morphology has been achieved. (C) In some animals, such as planarian flatworms, even tiny pieces of the body can determine what is missing and how to rebuild it, resulting in a perfect little worm each time. Not only does the regeneration stop when a correct planarian is rebuilt, they also avoid body-level aging indefinitely (Cebrià et al., 2018). (D) Tadpoles created with their craniofacial organs in abnormal configurations still largely metamorphose into normal frog faces, as the eyes, jaws, nostrils, etc. move around in novel paths (sometimes overshooting their target position before correcting) in order to reach the standard frog target morphology (Pinet et al., 2019; Vandenberg et al., 2012). The examples shown in panels A–D illustrate that multicellular bodies can execute not only feed-forward emergent morphogenesis that executes hardwired steps leading from gene activity to anatomical endpoints, but also an error minimization process that can achieve specific regions in morphospace (the target morphology) despite diverse starting configurations or external perturbations along the way (which can be caused by mutations, teratogens, microbiota, injury, etc.). (E) This process, known as anatomical homeostasis, results from cells' cooperating and competing to implement a "swarm behavior" that exhibits considerable robustness and plasticity (Harris, 2018; Pezzulo and Levin, 2015, 2016). The process of embryonic morphogenesis and adult morphostasis/regeneration is thus an example of problem-solving and goal-directed activity by a collective (Ben-Jacob, 2009; Couzin, 2007, 2009; Deisboeck and Couzin, 2009). While many feedback loops are known in biochemical and biomechanical morphogenetic control processes, bioelectric signaling (Durant et al., 2017; Levin, 2021) has been

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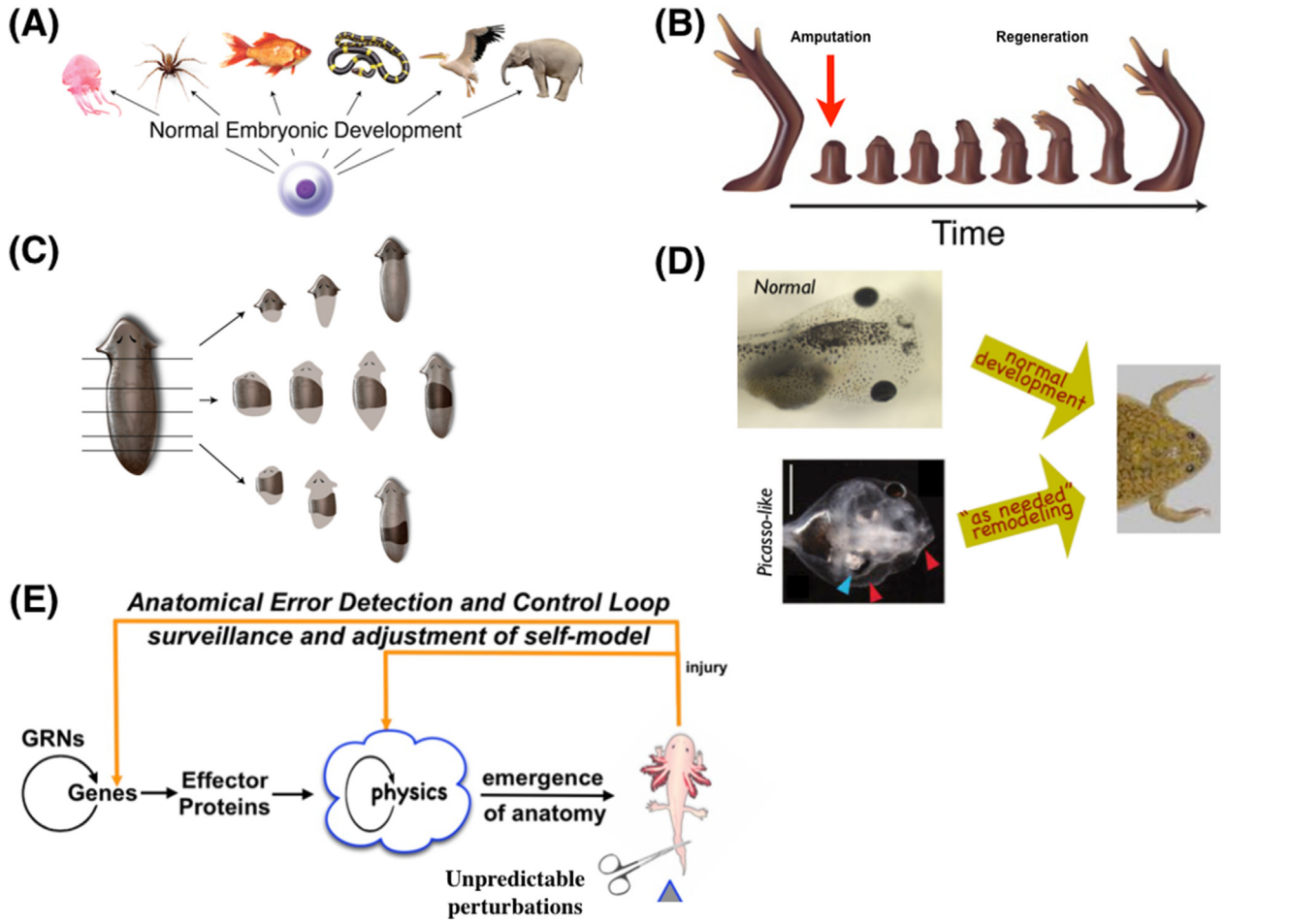

Fig. 1. Multicellularity binds cells toward large-scale morphogenetic goals.

particularly implicated in the storage and interpretation of the anatomical setpoint information with respect to which the homeostatic process regulates cell behavior to correct error. Thus it is no accident that bioelectric signals play an important role in the anatomical disorder aspects of cancer, where cells fail to obey the morphogenetic plan and undergo maladaptive growth that does not stop. Panels A,B,C are courtesy of Jeremy Guay of Peregrine Creative. Panel D is used by permission from (Vandenberg et al., 2011).

1.2. Cancer is a disruption of morphogenetic coordination (Fig. 2)

(A) Individual cells (unicellular organisms, or cells in culture) have a small spatiotemporal horizon of single cell-scale spatial perception, memory, and anticipation (Ford, 2017; Lyon, 2015). (B) Cells can connect into computational networks with greater spatiotemporal horizons, which enable the tissue to internally represent larger-scale goals (such as morphogenesis of organ-level structures, whose properties are not defined at a single cell scale) (Levin, 2019). Disruption of this connectivity shrinks the computational boundary of the goals towards which biological systems, such as cells, strive. In vivo, this results in cells defecting from the bodyplan and operating as unicellular organisms within the body they treat as external environment. (C) The coordination of cells into networks is mediated by a set of biophysical components of a morphogenetic field of instructive patterning information (Beloussov, 2001, 2015; Levin, 2012; Morozova and Shubin, 2013), which include biochemical gradients, biomechanical force fields, and bioelectrical signaling. Recent work has especially begun to unravel mechanisms by which these three modalities work together to process information (Nelson and Gleghorn, 2012; Petrik et al., 2018; Silver and Nelson, 2018; Silver et al., 2020; Smith et al., 2018). The morphogenetic field is critical at all phases of life, guiding embryogenesis, regeneration, and resistance to aging (Burr, 1940; Clark, 1995; Rubin, 1985; Waddington, 1935; Wolsky, 1978). Problems with cellular perception of this morphogenetic field can cause cells to revert to their unicellular evolutionary past (Bussey et al., 2017; Cisneros et al., 2017; Zhou et al., 2018), in which they treat the rest of the body as external environment and migrate/proliferate at will (Moore et al., 2017). In this model, the tumor cells are no more selfish than normal cells; the "Self" which is maintained shrinks from a body-scale structure to that of a single cell. Panels A,B are courtesy of Jeremy Guay of Peregrine Creative.

1.3. Importance of physiological controls of growth and form (Fig. 3)

Despite all the progress in molecular biology of stem cell activity during regeneration (Peiris et al., 2012; Reddien et al., 2005; Roberts-Galbraith and Newmark, 2013; Wagner et al., 2011), very fundamental gaps in our knowledge remain. (A) For example, if the stem cells of two species of planaria with round (red) and flat (green) head shapes are mixed in the same body, what head shape would be produced? No existing model makes a prediction on this

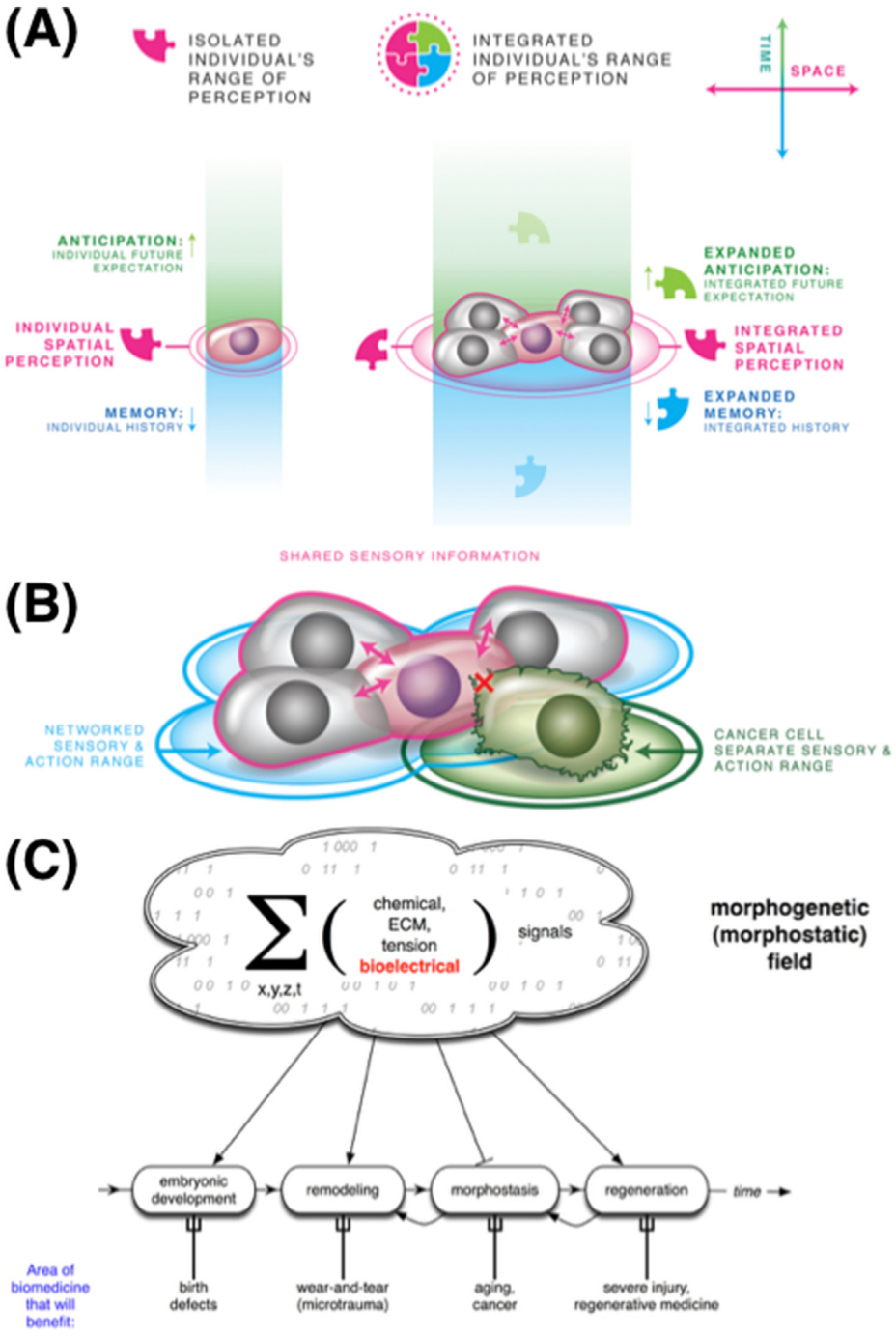

Fig. 2. Cancer is a disruption of morphogenetic coordination.

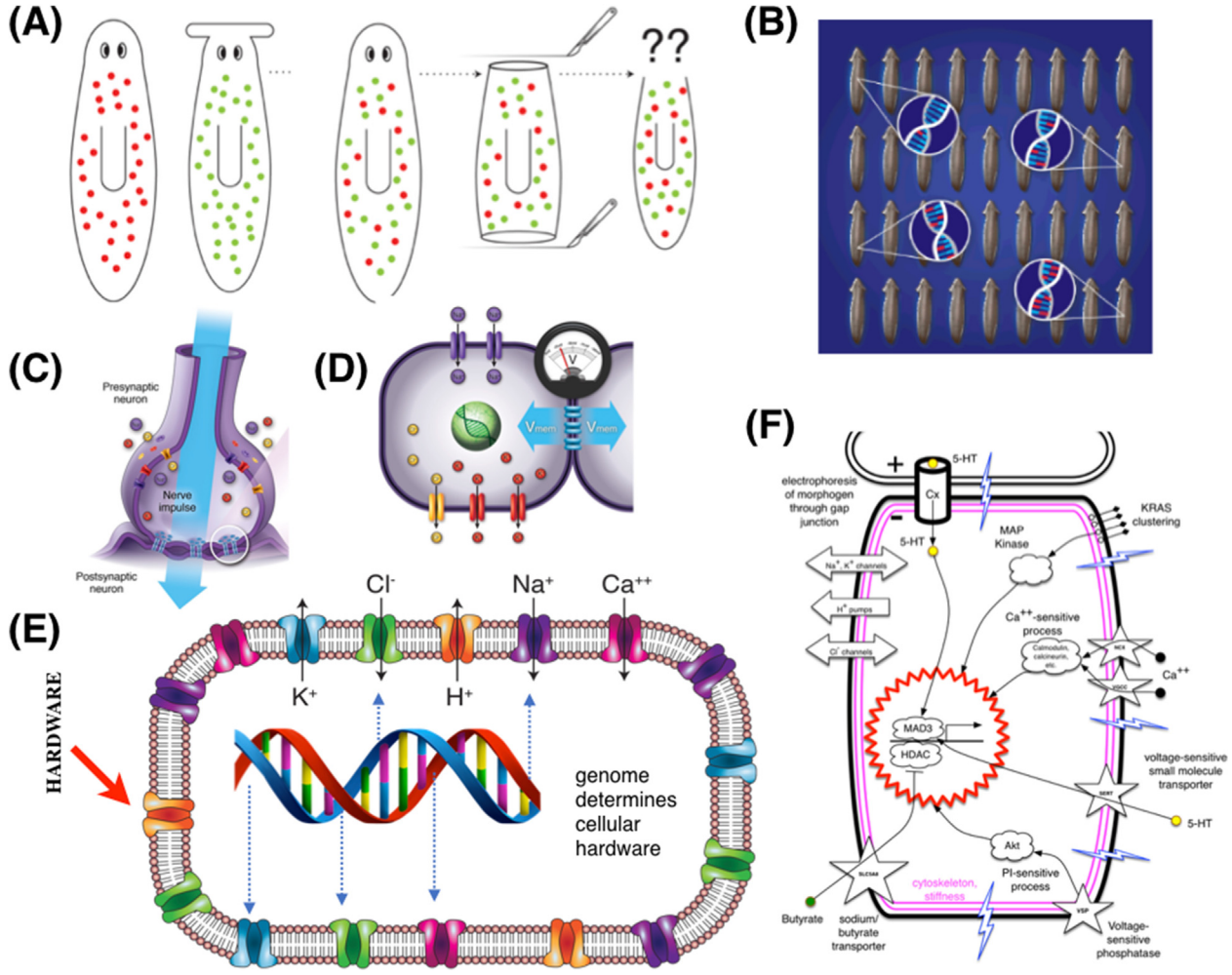

Fig. 3. Importance of physiological controls of growth and form.

experiment because while we have much detail about individual cell phenotypes, it's still unknown how cell collectives make decisions about which kind of anatomical shapes makes them stop remodeling. (B) A similar problem with respect to the relationship of the genome to the anatomy is illustrated by the fact that some species of planaria reproduce by fission and regeneration. This implements somatic inheritance, where any mutation that doesn't kill a neoblast propagates into the next generation. Thus, planaria exhibit massive genetic heterogeneity throughout their bodies (even mixoploidy), and yet offer 100% fidelity with respect to anatomical outcomes (Leria et al., 2019; Levin et al., 2018; Nishimura et al., 2015). These examples illustrate the gulf separating genetics and the control of anatomical phenotypes. An important aspect of the physiological layer between the genome and the body pattern is bioelectricity, which operates similarly in the brain and the rest of the body; like neurons, which use ion channels to set electric state and electric synapses known as gap junctions to propagate it to their connected cells (C), all cells likewise use ion channels to set their resting potential or V_{mem} and share it with neighbors (D). Thus, while the genome sets the cellular hardware (ion channels, transporters and pumps, and gap junctions), the bioelectric state is a complex function of the cell's history (experiences), environment, and signals from other cells (E). Consistent with this is the long-known importance of gap junctions for resisting transformation (Krutovskikh and Yamasaki, 1997), and the more recent emphasis on the cancer-neuron synapse in particular (Venkataramani et al., 2019; Venkatesh et al., 2019; Wirsching and Weller, 2020; Zeng et al., 2019). Cells' bioelectric states are transduced by a set of mechanisms such as neurotransmitter gating, calcium signaling, voltage-sensitive phosphatases, etc. (F) into second-messenger cascades that ultimately regulate gene expression required for specific morphogenetic events. It is essential to understand the connection between the genetically-determined cellular hardware and the physiological software of multiscale coordination, in order to discover definitive solutions to the cancer problem focused on normalizing and reprogramming cell activity (Costa et al., 2009; Kasemeier-Kulesa et al., 2008; Lawrence et al., 2011; Telerman et al., 2010), as a complement to current strategies focused on toxic chemotherapies. Panels A,B,C,E are courtesy of Jeremy Guay of Peregrine Creative.

1.4. Single cell bioelectrics assemble into networks (Fig. 4)

(A) A survey of bioelectric state across tissues (Binggeli and Weinstein, 1986; Srivastava et al., 2020) reveals that terminally-differentiated, quiescent, somatic cells tend to be hyperpolarized, while plastic and proliferative embryonic, stem, and cancer cells tend to be depolarized. Importantly, this is not just a correlation — V_{mem} is determinative. As early as the 1970's, it was already known that artificial depolarization can induce proliferation even in

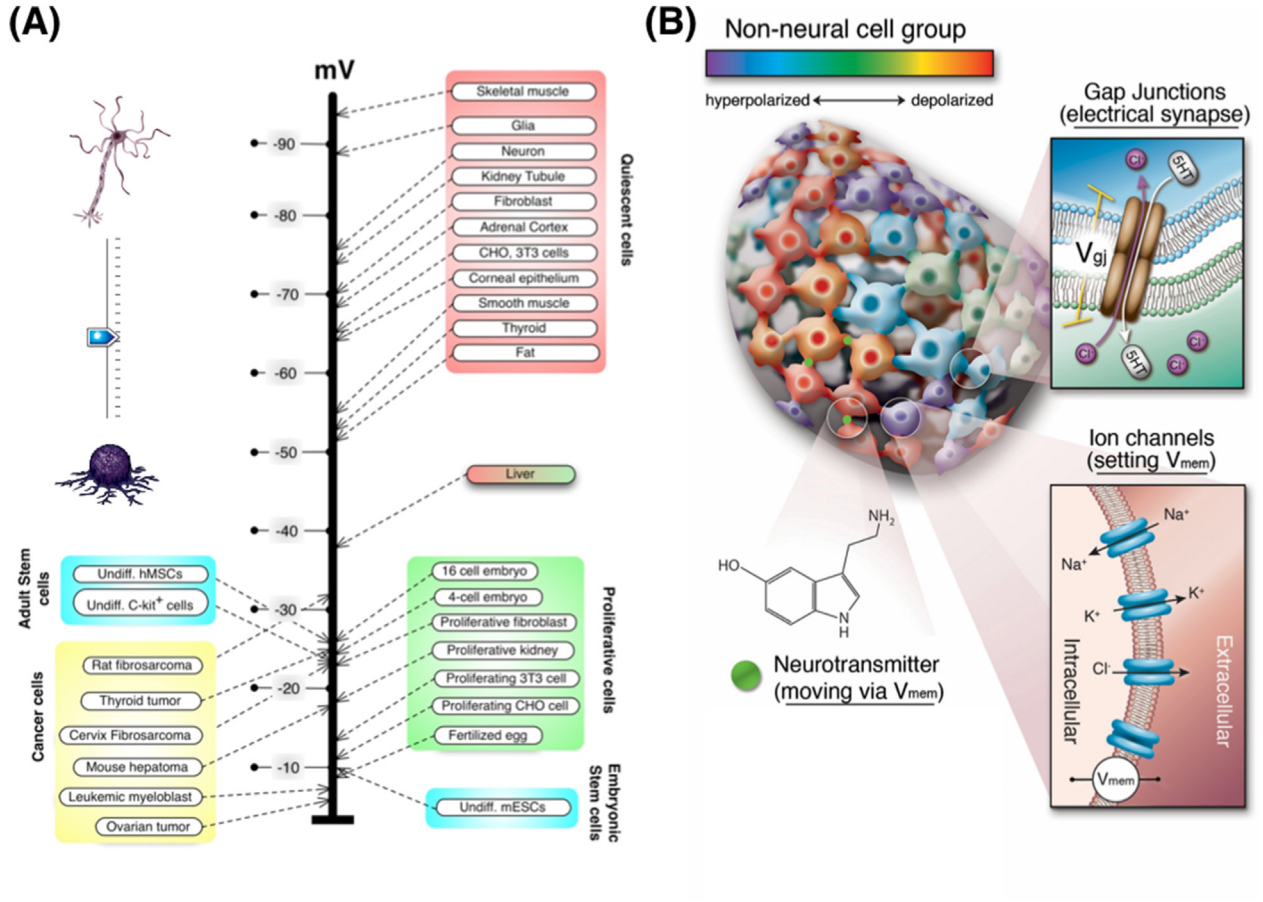

Fig. 4. Single cell bioelectrics assemble into networks.

mature neurons (Cone, 1980; Cone and Cone, 1976, 1978a, 1978b). (B) Crucially, anatomical outcome is not just a function of single cell V_{mem}, but rather the result of tissue-level computation. Networks of cells propagate complex patterns of bioelectric state, offering intervention in 3 main ways: modulating gap junctional connections (controlling the topology of the network), opening or blocking ion channels (regulating the actual V_{mem} of any given cell), and altering the movement of signaling molecules like serotonin, which are often redistributed downstream of bioelectrical signaling. In addition to cellular-level bioelectric states – V_{mem} - an important aspect of cancer is also tissue-level bioelectricity, such as transepithelial electric fields (Forrester et al., 2007) that serve as vector cues for electrotaxis of cancer cells (Brackenbury, 2012; Ding et al., 2008; Djamgoz et al., 2001; Huang et al., 2009; Sun et al., 2012; Yan et al., 2009; Yang and Brackenbury, 2013). Panel A is modified after (Binggeli and Weinstein, 1986). Panel B is courtesy of Jeremy Guay of Peregrine Creative.

1.5. Bioelectric state instructs cellular behavior during morphogenesis (Fig. 5)

Spatiotemporal patterns of V_{mem} *in vivo* are instructive for coordinating cell proliferation, differentiation, migration, and gene expression toward specific morphogenetic outcomes – the same processes that go awry in cancer. (A) mRNA encoding Kir6.2 ion channels microinjected into blastomeres of frog embryos induce a bioelectric state similar to the native eye field (Pai et al., 2012). When targeting precursors of gut or other tissues, eye tissue and whole eyes can be induced, which have all the correct internal tissues (A′), in locations that are otherwise not competent to become eye when induced by the "master" eye gene Pax6. (B) In regenerating planaria, fragments exhibit bioelectric gradients that are detectable by fluorescent voltage reporter dyes (Adams and Levin, 2012a, 2012b; Oviedo et al., 2008). Targeting (via pharmacological or RNAi approaches) the native ion conductances responsible for these gradients enable predictable changes to the anatomical outcome in the regenerate, including viable two-head or no-head forms (Beane et al., 2011). (C) Optogenetics (Adams et al., 2014) can be used in transgenic animals expressing light-activated ion pumps to induce whole ectopic limbs in aberrant locations such as the head. The importance of endogenous ion channels for this process has been observed in numerous channelopathies of embryogenesis (reviewed in (Srivastava et al., 2020)) as well as in the implication of ion channels as oncogenes (Table 1); this was presciently predicted by Burr in the 1930's (Burr, 1941; Burr et al., 1940). Panels A,A′ are used with permission from (Pai et al., 2012). Images in panel B were produced by Taisaku Nogi and Junji Morokuma, Levin lab. Panel C was produced by Erin Switzer, Levin lab.

1.6. Tumors are revealed by their abnormal bioelectric signature (Fig. 6)

It has been known for decades that tumorigenesis begins with the bioelectric decoupling of cells from the somatic morphogenetic network (Aasen et al., 2003; Kandouz and Batist, 2010; Leithe et al., 2006). One factor that can induce this is depolarization (reviewed in (Lobikin et al., 2012; Srivastava et al., 2020; Sundelacruz et al.,

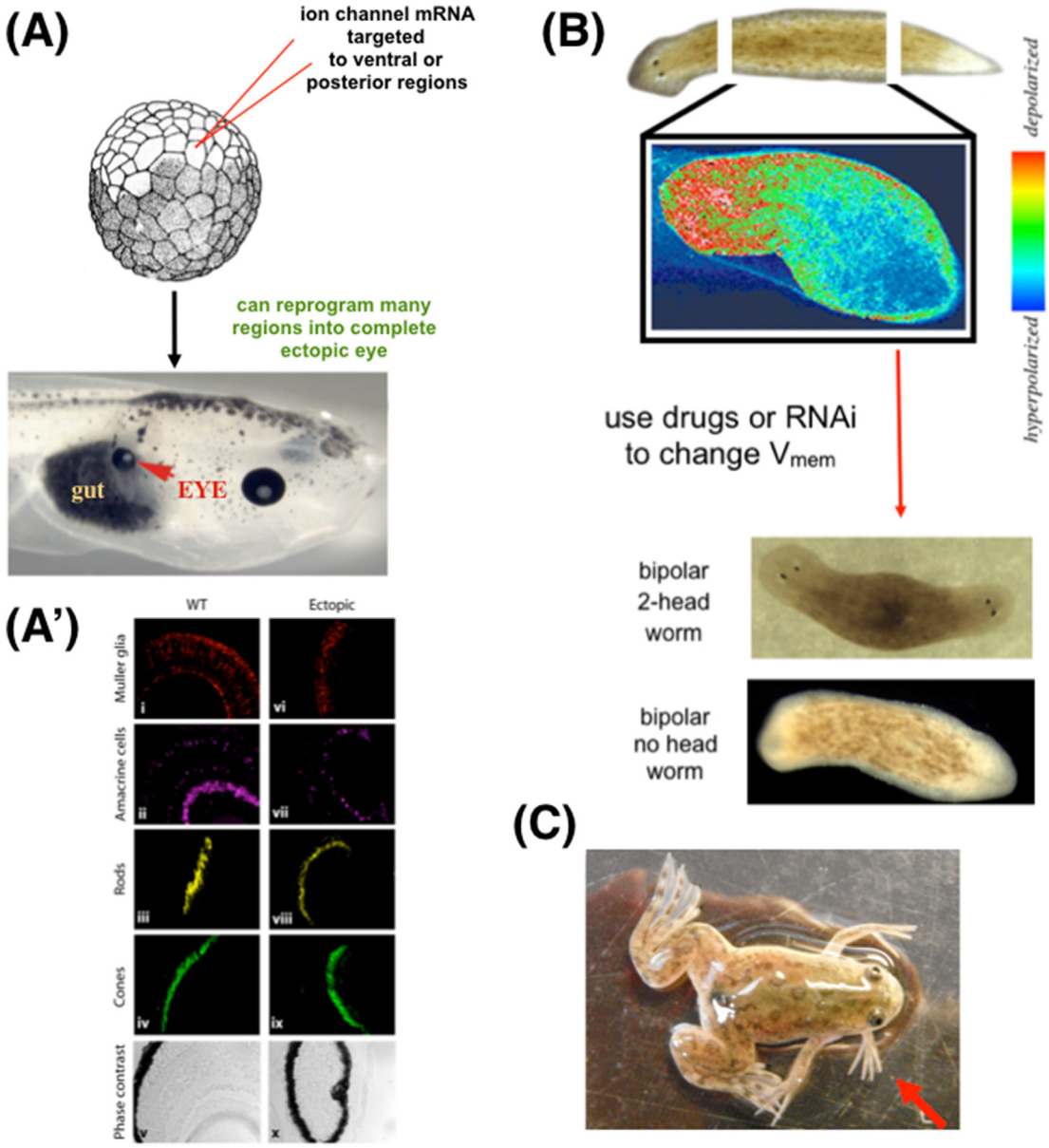

Fig. 5. Bioelectric state instructs cellular behavior during morphogenesis.

Table 1
Ion channel oncogenes.

Ion Translocator Protein	Species	Reference	
NaV1.5 sodium channel	Human	(House et al., 2010b; Onkal and Djamgoz, 2009)	Oncogene
KCNK9 potassium channel	Mouse	(Pei et al., 2003)	Oncogene
Ductin (proton V-ATPase component)	Mouse	(Saito et al., 1998)	Oncogene
SLC5A8 sodium/butyrate transporter	Human	(Gupta et al., 2006)	Oncogene
KCNE2 potassium channel	Mouse	(Roepke et al., 2010)	Oncogene
KCNQ1 potassium channel	Human, mouse	(Lee et al., 1997; Than et al., 2013; Weksberg et al., 2001)	Oncogene
NHE sodium/proton exchanger	Mouse	(Reshkin et al. 2000; Brisson et al., 2013; Loo et al., 2012)	Oncogene
SCN5A voltage-gated sodium channel	Human	(House et al., 2010a)	Oncogene
Metabotropic glutamate receptor	Mouse, Human	(Martino et al., 2012; Song et al., 2012; Speyer et al., 2012)	Oncogene
CFTR chloride channel	Human	(Xie et al., 2013; Zhang et al., 2013)	Tumor suppressor
Connexin43	Human	(Sirnes et al., 2012)	Tumor suppressor
BKCa	Human	(Schickling et al., 2015)	Oncogene
Acetylcholine receptor	Human, mouse	(Felder et al., 1993)	Tumor suppressor

2009)), which can be observed in tadpoles using voltage-sensitive fluorescent dyes (A, B, green and red signals) that reveal the location of nascent tumors (C, D) induced by microinjection of human oncogene mRNA (Chernet and Levin, 2013b). Thus, bioelectric state is a promising modality for non-invasive detection of pre-cancer and tumor margins during surgery. Panels A–D used with

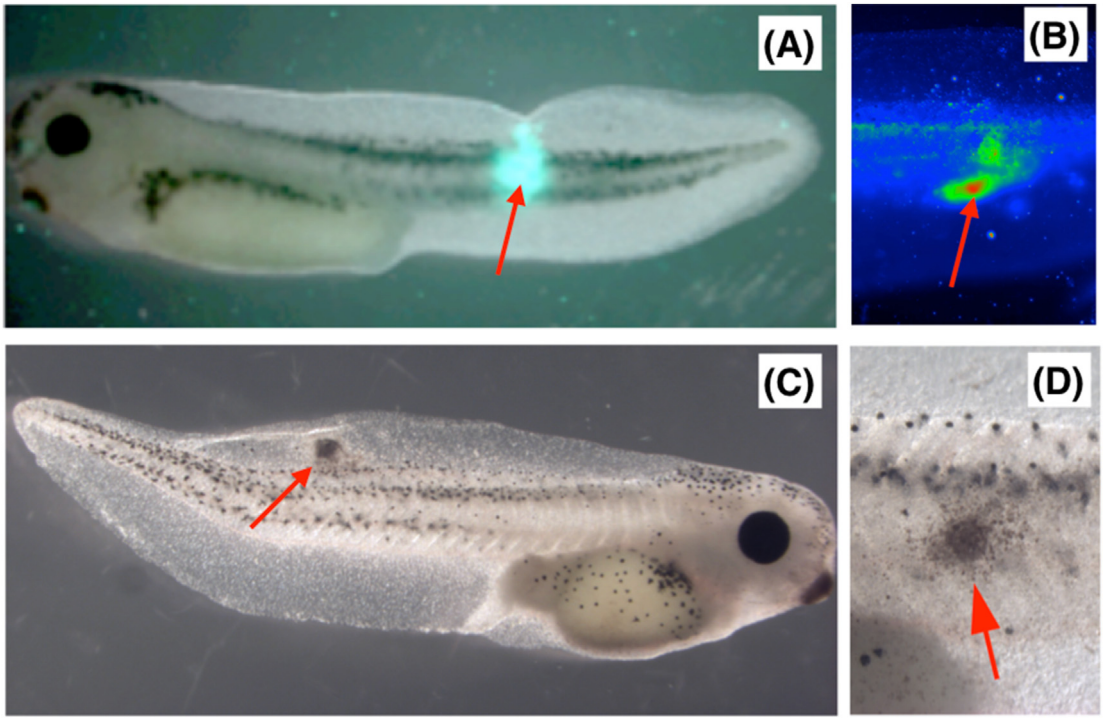

Fig. 6. Tumors are revealed by their abnormal bioelectric signature.

permission from (Chernet and Levin, 2013a).

1.7. Induction of metastatic melanoma phenotype by dysregulating bioelectric signals (Fig. 7)

The role of bioelectrics in keeping cells orchestrated toward normal morphogenesis and away from tumorigenesis is seen in loss-of-function studies targeting cells whose bioelectric state normally suppresses cancer-like behavior *in vivo* (Blackiston et al., 2011; Lobikin et al., 2012; Morokuma et al., 2008). For example, in tadpoles, normal pigment cells known as melanocytes have a characteristic shape (black cells) and are predominantly found above the brain and not in the space between the brain and eyes (A). In contrast, embryos exposed to the chloride channel opener

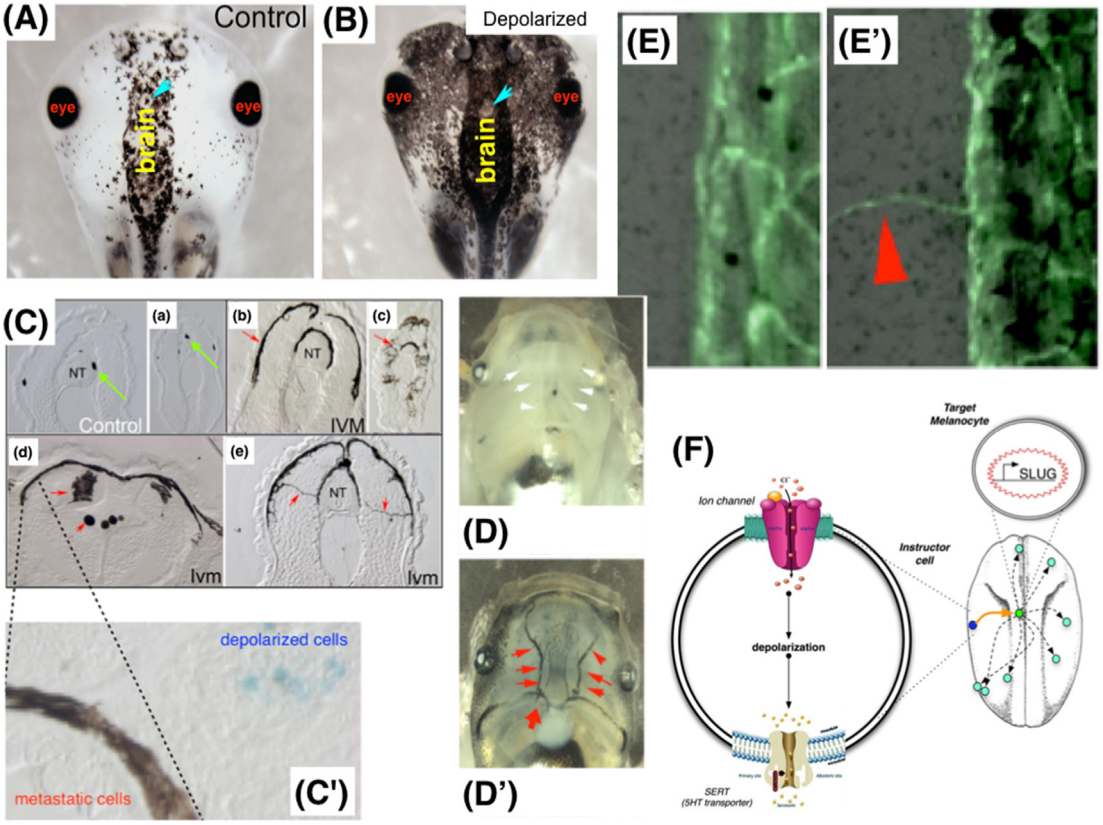

Fig. 7. Induction of metastatic melanoma phenotype by dysregulating bioelectric signals.

drug Ivermectin (IVM) that disrupts the V_{mem} of a special set of cells (instructor cells), in the absence of oncogenic mutations or carcinogens, transforms melanocytes to a metastatic phenotype. They over-proliferate, and spread across the head (B). In cross-section of the neural tube (NT), it is seen that compared to normal melanocytes which are round and occur in small numbers (C, Ca), animals with depolarized instructor cells show large numbers of melanocytes with a very abnormal stringy morphology (Cb, Cc). Moreover, these cells invade the neural tube lumen and brain (red arrows in Cd) and have highly abnormal invasive projections (Ce, red arrowheads). NT = neural tube. (C′) Importantly, the cells whose bioelectric state is manipulated (labeled with blue stain) are not the same cells as the ones that convert (brown cells) – this is a non-cell-autonomous effect showing the importance of the microenvironment to determine cancer-relevant phenotypes. A ventral view shows that compared to controls (D, white arrows indicate major blood vessels), embryos with depolarized instructor cells show extensive colonization of the blood vessels with the transformed melanocytes (D′) – a familiar part of the melanoma phenotype. Similarly, compared to the normal vasculature seen in wild-type tadpoles (E, green signal is fluorescent marker of blood vessels), depolarized animals exhibit frequent ectopic blood vessels (E′, red arrowhead). (F) Functional dissection of the signaling revealed a pathway in which the bioelectric state of instructor cells regulates their ability to signal to the melanocytes with serotonin. When dysregulated, this serotonergic signaling activates metastasis markers like SLUG and induces metastatic behavior that leads to over-proliferation and colonization of body organs (Blackiston et al., 2011). Importantly, this phenotype is induced with no chromosome damage or mutation, providing further evidence of the non-genetic origins of at least some cancers (Sonnenschein and Soto, 2016; Sonnenschein et al., 2014; Soto and Sonnenschein, 2014). Panels A–D′,F are used with permission from (Morokuma et al., 2008) and (Blackiston et al., 2011). Panels E,E' are used with permission from (Lobikin et al., 2012). Embryo section in panel F is

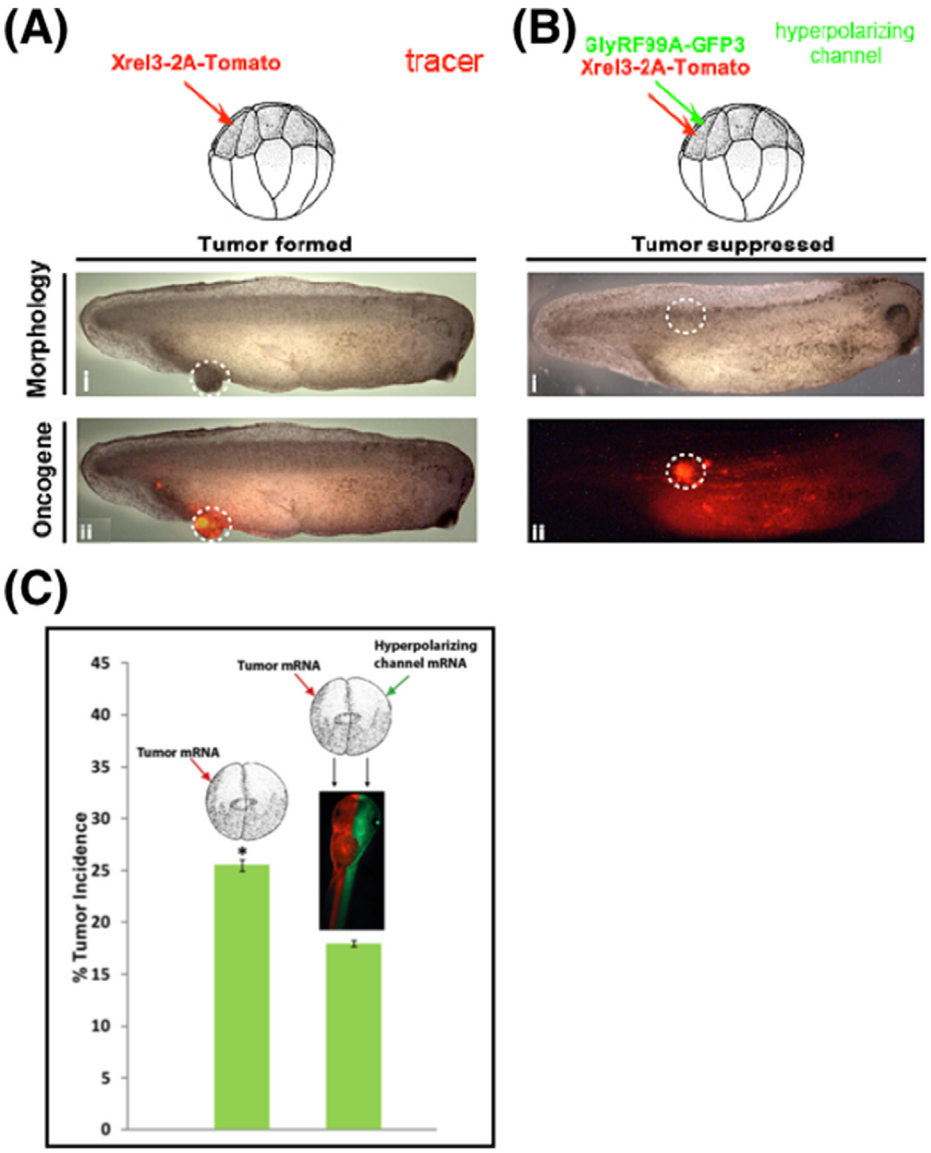

Fig. 8. V_{mem} state dominates carcinogenic mutation phenotypes.

1.8. V_{mem} state dominates carcinogenic mutation phenotypes (Fig. 8)

Appropriate bioelectric state can not only induce metastatic behavior, but it can also suppress tumorigenesis. (A, white dashed circles) mRNA encoding human oncogenes such as Xrel3 or KRAS mutations induce tumor structures in tadpoles (Ai, with red fluorescent marker on the oncoprotein in Aii) (Chernet et al., 2016; Chernet and Levin, 2013b). (B) Co-injection of a hyperpolarizing ion channel prevents tumor formation (Bi) despite the strong expression of the oncoprotein (fluorescently labeled with red signal, Bii). Importantly (C), this suppression works just as well when the channel is injected on the opposite side of the embryo, revealing (as with the melanoma phenotype) that it is the voltage of the environment that is critical for cell coordination away from tumorigenesis (Chernet et al., 2015; Chernet and Levin, 2014). The long-range control is modulated by bioelectric control of the movement of bacteria-derived butyrate (Chernet and Levin, 2014). As with the melanocyte phenotypes, these data illustrate the dissociation between the genetic state and the anatomical outcome, as these animals bear a strong oncogenic mutation which would predict the presence of a tumor, but the actual outcome depends on the physiological state that is not determined by the genetics (Levin, 2014; Sonnenschein and Soto, 2011; Soto and Sonnenschein, 2011). Panels A,B are used with permission from (Chernet and Levin, 2013b).

1.9. Computational approaches to manipulating bioelectric cancer phenotypes (Fig. 9)

One fascinating aspect of the bioelectric induction of the melanoma phenotype is that it occurs on an all-or-none basis: any given tadpole is either normal or completely transformed — all of the cells make the same, coordinated decision about whether to convert or not. At the same time, any given treatment is stochastic in a cohort of animals, causing for example 30% of them to transform and leaving 70% as wild-type. This illustrates the importance of large-scale decision-making in cancer, which is not a single-cell disease but a disorder of cellular coordination (Prehn, 1994, 1997; Tarin, 2012, 2013). In order to understand this body-wide phenotype, computational models can be constructed (A) of the known molecular components in the cascade of serotonergic signaling that underlies the depolarization-induced melanoma outcomes. Such models can be parametrized by a machine learning approach that fits network behavior to the precise stochastic outcomes identified in experiments (Lobikin et al., 2015; Lobo et al., 2017). Then, such models can be tested against candidate perturbations (e.g., drugs) in silico, to identify the rare combination of stimuli (B, red arrow) that would induce desired outcomes, such as breaking the coordination among cells (resulting in heretofore unseen animals in which only some of the cells had converted, while others remained normal). Dynamical system portraits (C,D) of such systems are important guides to understand large-scale behavior of such circuits, which can include decisions in state space (formed by the various levels of key molecules or V_{mem}) that are bifurcations — dynamics with extreme sensitivity to local conditions which become amplified into diverse outcomes (normal vs. metastatic) that appear stochastic. Such aspects of these circuits are not apparent from inspection of the molecular pathway models, and can be discovered by machine learning techniques (Lobikin et al., 2015; Lobo et al., 2017); understanding the stochastic aspects of physiological and transcriptional circuits is essential to understand the functional heterogeneity in patients with respect to cancer risk, treatment efficacy, and side-effects of possible therapeutics. Panels A–D are used with permission from (Lobikin et al., 2015; Lobo et al., 2017).

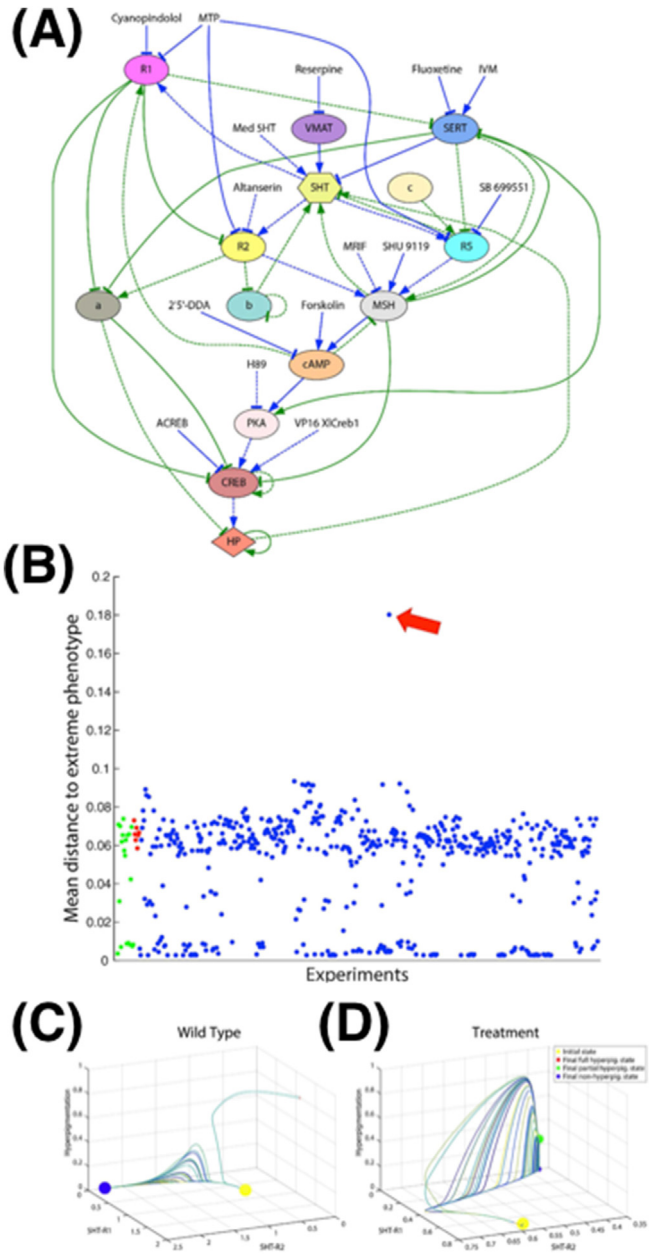

Fig. 9. Computational approaches to manipulating bioelectric cancer phenotypes.

1.10. An electroceutical approach to cancer (Fig. 10)

A roadmap (A) is proposed for future approaches to cancer and other disorders in which desired bioelectric state of specific tissues can be induced by drugs inferred by computational modeling software (Cervera et al., 2014, 2016; Pietak and Levin, 2016, 2017). A key next step is inference of which known channel drugs (electroceuticals) need to be used to open and close the correct channels to repair the normal bioelectric network state (Churchill et al., 2018). Examples of this approach include the use of computational bioelectric models to identify HCN2 channel opener drugs as an effective treatment to rescue both genetic (NOTCH mutation) and pharmacological (teratogenic) brain damage (Pai et al., 2015a, 2015b, 2018, 2020). One such system (B) called EDEn is coming online to help design drug blend approaches for cancer and other channelopathies (a current version is available at http://34.215.62.

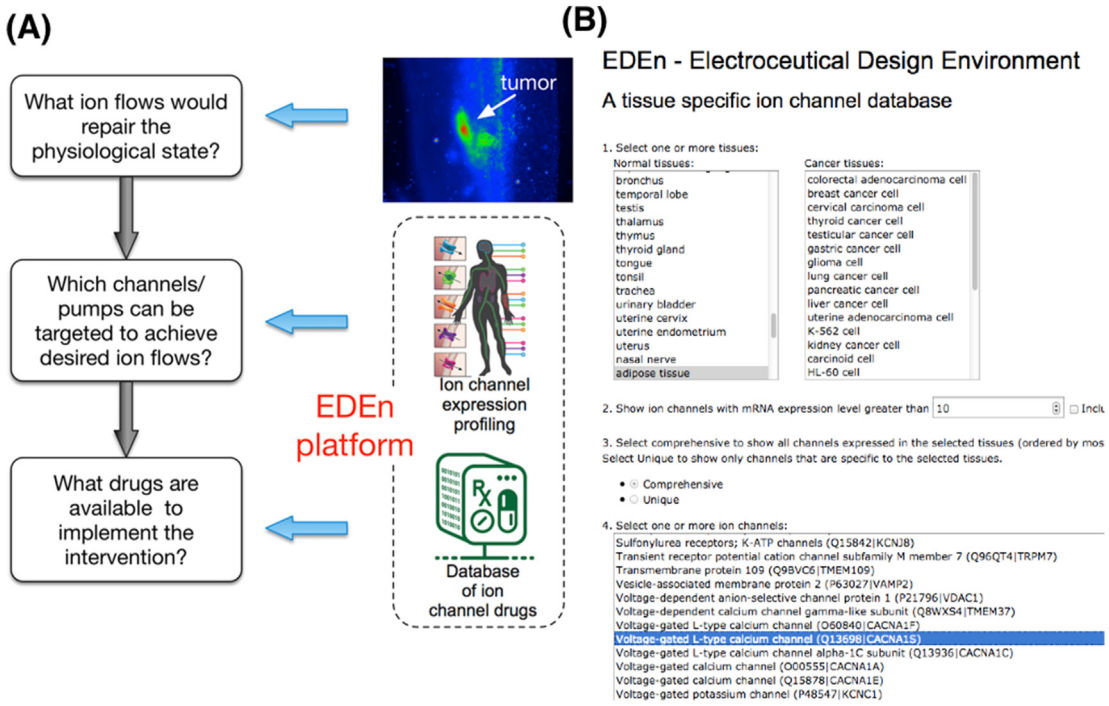

Fig. 10. An electroceutical approach to cancer.

180/db/). Panel in B was produced by Philip Winter and Jack Tuszynski. Panel A used with permission from (Churchill et al., 2018).

Author statement

Michael Levin is the only author of the manuscript.

Declaration of competing interest

The author declare no competing interests.

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