

A Voltage-Responsive Synthetic Cl- -Channel Regulated by pH

Shao-ping Zheng, Ji-jun Jiang, Arie van Der Lee, Mihail Barboiu

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A Voltage-Responsive Synthetic Cl⁻-Channel Regulated by pH 4 $\,$ A Voltage-Responsive Synthetic Cl~-Channel Regulated by pH 14 $\,$ 4 5 5

Shao-Ping Zheng, [Ji-Jun Jiang,](http://orcid.org/0000-0001-9483-6033) [Arie van der Lee, and](http://orcid.org/0000-0002-4567-1831) [Mihail Barboiu*](http://orcid.org/0000-0003-0042-9483) 6 6 7 7

inspiration for the design of artificial ion channels. Their across the cell membrane. Herein, we report that the aminobilayers. The alignment of water/Cl⁻ wires influences the conduction of ions, envisioned to diffuse along the hydrophilic 20 *uration, which can be greatly activated by applying strong* are reported in the literature.^[56–58] artificial ion-channels, parallel to that of biology. \blacksquare Abstract was shortened to fit within allotted space. \blacksquare

 27 the ion transport across the cell membrane maintaining most responsive channel. The formation of ion channels was 27 28 of the vital functions.^[6-10] Any defects of these systems would evidenced by X-ray crystal structures of **Imu-2** and **Imu3-** 28 cause specific diseases related to disorders of ion flux, 30 clinically called *channelopathies*.^[11–15] For instance, cystic conductance profile. These columnar aggregates different 30 fibrosis (CF) is associated with defective Cl^- conductance 32 along CFTR channel due to unexpected mutations.^[16,17] reasons to be considered as dually pH/voltage-triggered 32 33 Synthetic ion transporters have greatly emerged in recent biomimetic Cl⁻ channel with high performance in bilayer 33 34 decades, as novel treatment approaches to replace the membranes. Interestingly, the channels show pH and voltage- 34 35 deficient proteins with structurally simpler compounds to dual responsive properties, with ion transport activated under 35 36 effectively restore the transport biofunction.^[18-21] Inspired by low and high pH (with no activity at intermediate) and the 36 37 prodigiosin, a natural H⁺/Cl⁻ carrier with potent anticancer application of a high membrane potential. The dual-respon- 37 38 activity,^[22–25] studies toward active synthetic transporters open siveness is an important merit of the work, which remains as 38 39 up new avenues for the development of antitumor agents.^[26–29] a previously unreported behavior and would surely inspire 39 40 Compared with extensively documented Cl⁻-carriers/iono- future research in this area. 40 pathway, remain rare. 29 cause specific diseases related to disorders of ion flux, **HCl**, as well as planar lipid bilayer assays showing step-like 29 31 fibrosis (CF) is associated with defective Cl⁻ conductance from other stimulus-activated channels^[59–66] provide excellent 31

Natural channels present frequent open-closed transi-

 8 **Abstract:** Transmembrane protein channels are an important agents, to generate action potential as signal transduction. 8 10 dipolar structure helps overcome the high energy barrier to in human nuclear membranes is a class of voltage-sensitive 10 11 selectively translocate water and ions sharing one pathway, CI -channel which widely performs in transepithelial ion 11 13 imidazole (Imu) amphiphiles self-assemble via multiple H - CLIC1 exists in two forms into lipid bilayers, either as soluble 13 14 bonding to form stable artificial CI⁻-channels within lipid monomers,^[52] or as an active CI⁻ channel, built through a pH- 14 17 pathways; at acidic pH, Cl⁻/H⁺ symport conducts along a concentration-dependent oligomerization event, resulting 17 18 a partly protonated channel, while at basic pH, higher Cl⁻/ in the formation of a voltage-responsive Cl⁻ channel. How-19 OH⁻ antiport translocate through a neutral channel config- ever, few examples of voltage-responsive synthetic channels 19 agents, to generate action potential as signal transduction. $\%$ inspiration for the design of artificial ion channels. Their CLIC (Intracellular Chloride Channel) protein family found $\%$ in human nuclear membranes is a class of voltage-sensitive Cl--channel which widely performs in transepithelial ion 12 across the cell membrane. Herein, we report that the amino-
absorption and secretion in the kidney.^[51] Among this family, 12 CLIC1 exists in two forms into lipid bilayers, either as soluble monomers,^[52] or as an active Cl^- channel, built through a pH-15 bilayers. The alignment of water/Cl⁻ wires influences the dependent state transition from soluble CLIC1.^[53] Determi-16 conduction of ions, envisioned to diffuse along the hydrophilic nation of CLIC1 structure in the membrane^[54,55] confirms 16 a concentration-dependent oligomerization event, resulting in the formation of a voltage-responsive Cl⁻ channel. However, few examples of voltage-responsive synthetic channels are reported in the literature.[56–58]

21 electric field. This voltage/pH regulated channel system Herein, we report a series of amino-imidazole (Imu) 21 22 represents an unexplored alternative for ion-pumping along amphiphiles that form self-assembled Cl⁻/water channels in 22 Transmembrane protein channels^[1–4] and carriers^[5] facilitate be greatly activated, simultaneously resulting in a voltage- $\frac{25}{26}$ Herein, we report a series of amino-imidazole (Imu) amphiphiles that form self-assembled Cl⁻/water channels in 23 *artificial ion-channels, parallel to that of biology.* \blacksquare Abstract the lipid bilayers. Similar to natural protein CLIC1's, [51-55] two 23 24 was shortened to fit within allotted space. \blacksquare different pH-dependent self-assembled channel configura- 24 $25 \rightarrow 25$ tions are found. Moreover, at high basic pH, Cl⁻ channel can 25 be greatly activated, simultaneously resulting in a voltageresponsive channel. The formation of ion channels was evidenced by X-ray crystal structures of Imu-2 and Imu3 conductance profile. These columnar aggregates different reasons to be considered as dually pH/voltage-triggered biomimetic Cl⁻ channel with high performance in bilayer membranes. Interestingly, the channels show pH and voltagedual responsive properties, with ion transport activated under low and high pH (with no activity at intermediate) and the application of a high membrane potential. The dual-responsiveness is an important merit of the work, which remains as a previously unreported behavior and would surely inspire future research in this area.

4 phores that translocate themselves across membrane,^[29–34] The reaction between substituted amino-imidazoles and 4 42 examples of synthetic Cl⁻-channels^[35-40] providing hydrophilic corresponding alkyl-isocyanates readily afforded compounds 42 43 interiors for successive ion hoping along selective conducting Imu1-3 (Figure 1). It's noted that electrophilic isocyanate 43 46 tions,^[41] usually relying on external triggers such as volt- imidazole with different electron-withdrawing side groups 46 47 age,^[42-44] light,^[45,46] temperature,^[47,48] redox^[49] or molecular^[50] results in the formation of more acidic C1-H groups 47 The reaction between substituted amino-imidazoles and corresponding alkyl-isocyanates readily afforded compounds Imu1-3 (Figure 1). It's noted that electrophilic isocyanate 44 pathway, remain rare. A series of the selectively reacted with N2-imidazole ring, which is 44 A 5 Natural channels present frequent open-closed transi- more nucleophilic than -NH₂ group. The 4-substitution of 45 imidazole with different electron-withdrawing side groups results in the formation of more acidic C1-H groups 48 **All Constanting Street Constanting Constanting Street Constanting Street Constanting Street Associates.** 48

 [*] Dr. S.-P. Zheng, Dr. J.-J. Jiang, Dr. M. Barboju Single-crystals of **Imu2** and **Imu3H⁺·Cl**⁻ were obtained by 49 Lehn Institute of Functional Materials, School of Chemistry, Sun Yat-slow evaporation of water/methanol or ethanol solution at 50 room temperature.[67] As shown in Figure 1, the single-crystal 51 51 guangzhou 5102/5 (China) E-mail: mihail-aumitru.barbolu@umontpellier.ir undergo self-assembly via extended H-bonding networks and 53 Dr. S.-P. Zheng, Dr. A. van der Lee, Dr. M. Barbour explorers form pores with water/anion wires arrays found inside. 54

 55 $\overline{}$ institute Lucleums Croup University of Monthologies $\overline{}$ analysis of $\overline{}$ Analysis of $\overline{}$ analysis of $\overline{}$ and $\overline{}$ crystal packing shows heteromeric $\overline{}$ $\overline{\phant$ bonding associations of interdigitated amino-imidazole ter-

Place E. Bataillon CC047, 34095 Montpellier (France) bonding associations of interdigitated amino-imidazole ter- 57 Supporting information and the ORCID identification number(s) for minal heads, interacting on one side with their neighbors via 57 58 **in** the author(s) of this article can be found under: four -CO···H₂N- $(d_{\text{N-H}} = 3.00 \text{ Å})$ H-bonds between Imu2 head 58 units, which presents an unusual tetrahedral geometry (Fig-59 59

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 $\frac{33}{2}$ Figure 1. Chemical structures of Imu1–3; a) X-ray single-crystal packing in stick representation of Imu2; b) X-ray single-crystal packing in stick $\frac{33}{2}$ 34 representation of Imu3H⁺·Cl⁻; c) top view and d) lateral view of the channels revealing the formation of the anion–water wires via synergetic N-H 34 and C-H hydrogen bonding. Anions are presented in ball model. 35 35

ure 1 a). In the crystal, zipper-like layers are formed, further 39 interconnected via double -N_{Im}···NHCO- H-bonds ($d_{N\text{-}H}$ = via multiple hydrogen bonding interactions: C-H···Cl⁻ ($d_{\text{c-H}}$ 39 3.00 Å) on the other side of $\text{Im}u\text{2}$ heads. The successive Hbonding sequences strongly enforce the channel-type winding 42 of Imu2 strands allowing considerable overlap between the vicinal alkyl chains. Moreover, bridging water molecules are 42 hydrophobic alkyl chains of the monomers. Therefore, the 44 intermolecular hydrogen bonding affords a preorganized interaction from O_2H —Cl (\approx 2.3 Å). channel-like structure with two unique lumens in turn aligned. 46 The robustness of the continuous alignment of **Imu2** results through channel may act as driving force for ion permeatio-46 from the compatibility and the simultaneous effect of Hbonding and hydrophobic interaction, which may be associated with the stable oligomers observed in membranes. 38 ure 1 a). In the crystal, zipper-like layers are formed, further superstructure is asymmetrically surrounding the Cl⁻ anions 38 40 3.00 Å) on the other side of **Imu2** heads. The successive H- $_{\text{Cl}} = 2.6 \text{ Å}$, -CONH \cdot ··Cl⁻ (d_{C-H-Cl} = 2.6 Å) and -CO-NH₂···Cl⁻ 40 4 bonding sequences strongly enforce the channel-type winding $(d_{\text{c+1-c}} = 2.8 \text{ Å})$, while the remaining space is closed by 4 1 43 hydrophobic alkyl chains of the monomers. Therefore, the present in this pocket as a result of strong anion-dipole 43 45 channel-like structure with two unique lumens in turn aligned. The alignment of water molecule-anion within single wire 45 47 from the compatibility and the simultaneous effect of H- n.^[40a, 58b] The water-anion wires within channels anticipate, to 47 48 bonding and hydrophobic interaction, which may be associ- some extent, the Cl⁻ transport activity responsive to outer pH 48 49 ated with the stable oligomers observed in membranes. change in the following transport experiments. There are 49

The single-crystal packing of protonated Imu3H⁺·Cl⁻, 5 reveals that one third of the molecules are protonated. They corresponding to acidic $[H_2O \cdot Cl^-]$ and basic $[OH^-H_2O \cdot Cl^-]$ 5 tend to assemble in a "head-to-head" conformation via 53 -CO···H₂N and -CO···N_{Im} H-bonds (d_{N-H} = 3.00 Å) between that complex protein anion-channels can be bio-mimicked 53 54 the Imu3 head units on one side, while double H-bonds via using simpler compounds displaying constitutional functions 54 55 -N_{Im}^{-••}NHCO- motifs (d_{N-H} = 3.00 Å) are formed on the other like the natural ones. 55 5 \degree side. Alternative H-bonding dimers form successive layers in The ion transport activities of Imu1–3 were fully inves- 56 57 tight contact with the neighboring ones. This assembled tigated across EYPC-LUVs (egg yolk phosphatidylcholine 57 pattern encapsulates water/chloride-wires filling the interior 59 void of about 5 Å in diameter (Figure 1b–d). The inner pore HPTS (8-hydroxypyrene-1,3,6-trisulfonate) and NaCl 59 52 tend to assemble in a "head-to-head" conformation via pH conditions. Our findings may be related to imagination 52 58 pattern encapsulates water/chloride-wires filling the interior large unilamellar vesicles)^[68] loaded with a pH-sensitive dye 58

via multiple hydrogen bonding interactions: C-H \cdot ··Cl⁻ ($d_{\text{c-H}}$ vicinal alkyl chains. Moreover, bridging water molecules are interaction from O₂H—Cl (\approx 2.3 Å).

through channel may act as driving force for ion permeatio-50 The single-crystal packing of protonated Imu3H⁺·Cl⁻, probably two different water/anion binding configurations 50 corresponding to acidic $[H_2O \cdot Cl^-]$ and basic $[OH^- \cdot H_2O \cdot Cl^-]$ that complex protein anion-channels can be bio-mimicked using simpler compounds displaying constitutional functions like the natural ones.

> The ion transport activities of Imu1–3 were fully investigated across EYPC-LUVs (egg yolk phosphatidylcholine HPTS (8-hydroxypyrene-1,3,6-trisulfonate) and NaCl

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(100 mM) and suspended in buffers (100 mM, MCl, $M^+ = Li^+$, 2 Na⁺, K⁺, Rb⁺, Cs⁺). While varying cation in the extravesicular 8.4 gradually neutralizes the protonated **Imu** channels and 2 3 buffer or introducing FCCP (carbonyl cyanide-4-(trifluoro-consequently weakens transport activity; c) at higher pH 8.4 \sim 3 4 methoxy)-phenylhydrazone) as H⁺ carrier didn't make any 11.4, the increased OH⁻ concentration introduces another 4 differences (Figure S6) 1 (100 mM) and suspended in buffers (100 mM, MCl, $M^+=Li^+$, activated via inner water wires [H₂O·Cl⁻]; b) increasing pH to 5 differences (Figure S6) **by The CLA** antiport mechanism favored by translocation of 5

A series of assays: HPTS $(10 \mu M)/NaCl$ $(100 \mu M, pH 6.4)$ 7 containing LUVs were suspended in the extravesicular buffer ing Cl⁻ transport efficiency. 8 solution (100 mM NaCl) with different pH values: 7.4, 8.4, 9.4, Pseudo-first-order initial transport rate constants are 8 9 10.4, 11.4), showed that the fluorescence ratio intensity strongly dependent on ΔpH (pH difference between intra- $\frac{10}{10}$ gradually improved, especially with a significant increase and extravesicular media) giving a transport rate sequence $\frac{10}{10}$ 11 from pH 8.4 to pH 11.4 implying a new translocation mech- $\text{Im}u3 \leq \text{Im}u1$ < $\text{Im}u1a$ < $\text{Im}u2$ with maximum transport rate 11 anism through assembled channels Imu1, Imu1a and Imu2, 13 respectively (Figure 2c,d \blacksquare Figure 2a,b? \blacksquare , S8). Imu3 fluorescence ratio change at the same ΔpH (Figures S8, S10 13 hardly showed transport activity irrespective of pH values 15 (Figure S8e), and control experiments of LUVs loaded with channel was shown much better than that in Imula-based 15 $\frac{1}{6}$ Na₂SO₄ (50 mM) instead of NaCl provided low transport channel with pH increase, though Imu1 a has higher transport $\frac{1}{6}$ activities of Imu channels (Figure S7). Interestingly, the Cl⁻ 18 transport activities-related fluorescence ratio changes of of water wires within $\text{Im}u\text{2-assembled}$ channel is evenly 18 19 Imu1 (Figure S10b), Imu1a (Figure S8c) and Imu2 (Fig- distributed along the whole hopping path, rendering a manner 19 20 ure S8d), dropped out when outer pH was changed from 7.4 of transport rate whose steady increase only depends on OH⁻²⁰ 21 to 8.4, then increased back to the maximum at pH 11.4. concentration. 21 22 Accordingly, the Cl⁻ transport is highly dependent on pH: a) The conductances of **Imula** or **Imu2** channels were 22 23 at lower pH values, Imu compounds are protonated under assessed by the bilayer clamp technique in 1 M KCl solution 23 weakly acidic condition, which then induces a Cl⁻/H⁺ symport 25 along the assembled channel, and the proton transport is after addition of compound solution, distinct channel opening 25 δ A series of assays: HPTS (10 μM)/NaCl (100 mM, pH 6.4) OH-anions [$\text{-OH-H}_2\text{O-Cl}$] within channels, greatly improv- δ 12 anism through assembled channels **Imu1, Imu1a** and **Imu2**, values at $\Delta pH = 5$ or 6, quite in accordance with their 12 14 hardly showed transport activity irrespective of pH values and Table S1). Meanwhile, Cl⁻ flow speed in **Imu2**-based 14 17 activities of Imu channels (Figure S7). Interestingly, the Cl⁻ activity (EC₅₀), also suggesting the cooperative translocation 17 24 weakly acidic condition, which then induces a Cl⁻/H⁺ symport as electrolyte with different pH values (4, 7, 8, 11). Thereby 24

Figure 2. a) Normalized fluorescence intensity versus outer pH for Imu1 a and Imu2, (insets) proposed transport mechanisms; b) pseudo-first-order initial transport rate constants for Imu1–3 versus Δ pH between intra- and extravesicular media.

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8.4 gradually neutralizes the protonated Imu channels and consequently weakens transport activity; c) at higher pH 8.4– 11.4, the increased OH⁻ concentration introduces another ing Cl⁻ transport efficiency.

Pseudo-first-order initial transport rate constants are strongly dependent on Δ pH (pH difference between intraand extravesicular media) giving a transport rate sequence Imu3 \ll Imu1 $<$ Imu1 a $<$ Imu2 with maximum transport rate fluorescence ratio change at the same ΔpH (Figures S8, S10 channel was shown much better than that in Imu1 a-based channel with pH increase, though Imu1 a has higher transport of water wires within Imu2-assembled channel is evenly distributed along the whole hopping path, rendering a manner of transport rate whose steady increase only depends on OH concentration.

The conductances of Imu1a or Imu2 channels were assessed by the bilayer clamp technique in 1 M KCl solution after addition of compound solution, distinct channel opening 26 and closing states confirmed the formation of **Imu1a**- or 26 27 **Imu2**- based channel (Figure 3a–h). **Imu2**'s multi-conductance channel is also reminiscent of the same channel 28 28 $29 \rightarrow 29$ characteristic of CLIC1 channel.^[69] 29

30 **30 120** 31 $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ more recorded at high pH 8 and 11 (Figure 3 c,d,g,h), while at 32 $\frac{1}{2}$ **PH** 4 and 7 (Figure 3 a,b,e,f) the lower level dominated at the 33 $\frac{96}{9}$ $\frac{1}{2}$ $\frac{96}{1}$ $\frac{1}{2}$ expense of the closed baseline state. I–V plots at different pH 34 values (Figure 3i,j) more obviously demonstrated a significant 35 35 $\frac{36}{2}$ $\frac{36}{2}$ $\frac{1}{27}$ $\frac{0.4}{27}$ $\frac{1}{27}$ $\frac{1}{27}$ from 4 to 11. The magnitude of the smallest openings 37 Observed at lower pH for protonated channel configuration 38 $\frac{29}{2}$ **is inferior to the regular activities of electroneutral channel** 39 40 $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ is configuration at basic pH. For both compounds, I–V plots 40 41 a ibi c iveled a linear variation (i.e., ohmic behavior) at low 41 42 **potential, while at higher potential they became asymmetric** 42 43 **and seemed greatly responsive toward either negative or** 43 14 $^{8.4}$ $^{11.4}$ positive voltage applied, especially at basic pH, leading us to 44 45 and Imu2-built channels are simultaneously 45 and Imu2-built channels are simultaneously 45 46 **Imulua Imula Imula** Imula Imula Imus **triggered by high voltage. This hypothesis is confirmed by the** 46 $\frac{1}{47}$ $\frac{1}{47}$ $\frac{1}{47}$ perfect fitting of current versus voltage curves with 2- $\frac{47}{47}$ parameter exponential function (Figure S13, S14) which 48 48 $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ represents a kind of sharp current increase with changing 49 $\frac{1}{2}$ \blacksquare voltage behavior. Usually ion transport property of a nano- 50 $\frac{51}{5}$ 50 $\frac{1}{5}$ $\frac{1}{5}$ $\frac{1}{5}$ $\frac{1}{5}$ channel relies on channel shape, channel surface charge 51 $\frac{1}{2}$ distribution, and the wettability of the channel.^[70] Multiple 52 conducting species illustrate "supramolecular polymorphism" 53 53 $54 \rightarrow$ 1 2 3 4 5 commonly observed with synthetic channel-forming com- 54 $\Delta \rho H$ $\Delta \rho H$ pounds.^[71] We therefore equate the lower Cl⁻/H⁺ symport 55 56 $\frac{3}{2}$ $\frac{1}{2}$ $\frac{1}{$ 57 Imula and Imu2, (insets) proposed transport mechanisms:
strong electrostatic interaction and the higher Cl⁻/OH⁻ 57 58 b) pseudo-first-order initial transport rate constants for Imul–3 versus antiport state with the same channel but in a form of single 58 59 Δ pH between intra- and extravesicular media. 59 hydrated anion species. Their orderly flow toward one 59

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Figure 3. Channel conductance of Imu1 a-based channel at pH a) 4, b) 7, c) 8, d) 11 and of Imu2-based channel at pH e) 4, f) 7, g) 8, h) 11; I–V 37 38 plots for i) Imu1a and j) Imu2 recorded in KCl solution at pH 4, 7, 8 and 11, respectively. 37 Figure 3. Channel conductance of Imula-based channel at pH a) 4, b) 7, c) 8, d) 11 and of Imu2-based channel at pH e) 4, f) 7, g) 8, h) 11; l-V 37

42 channel, which can certainly be stimulated if a strong electric in progress to pursue such studies. 42 43 field is applied. 43

44 In summary, we've designed an original class of synthetic 44 45 self-assembled chloride channels **Imu1–3** providing remark- **Acknowledgements** 45 able combination of functions very close to natural ones (i.e. 46 ± 46 47 CLIC1): synergetic pH regulation and voltage sensitivity. This work was supported by Centre National de la Recherche 47 Their signal sensitivity is related to the alignment of chloride-49 water single file along channel acting as driving force for interdisciplinaires (MITI), Défi Biomimetisme and Agence 49 50 permeating H₂O-mediated Cl⁻ transport and responding to Nationale de la Recherche ANR-18-CE06-0004-02, WATER- 50 5 pH change. At acidic pH, Cl⁻/H⁺ symport conducts along CHANNELS. S.-P. Zheng wishes to thank China Scholarship 5 a partly protonated channel mainly driven by hydrogen 53 bonding interactions. When switched to basic pH, higher Cl⁻/ Europeen des Membranes) for MS measurements. 53 OH- antiport hydrated anions are transported through 54 54 55 a neutral channel configuration, which can be greatly 55 56 activated by applying strong electric field. Conversely, the **Conflict of interest** 56 57 molecular-scale hydrodynamics of water and anions within 58 channels, could also provide inspirations for the systematic The authors declare no conflict of interest. 58 48 Their signal sensitivity is related to the alignment of chloride-
Scientifique, Mission pour les initiatives transverses et 48 52 a partly protonated channel mainly driven by hydrogen Council for the financial support. We thank E. Petit (Institut 52 59 59

41 direction creates a dynamic charge distribution along the rationalization of active stimuli responsive channels. Work is 41 rationalization of active stimuli responsive channels. Work is in progress to pursue such studies.

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Conflict of interest

The authors declare no conflict of interest.

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Communications

Ion Channels

S.-P. Zheng, J.-J. Jiang, A. van der Lee, M. Barboiu* _______________________ **IIII-IIII**

A Voltage-Responsive Synthetic Cl⁻-

Ion Channels

M. Barboiu* **______________ |||||-||||**

A Voltage-Responsive Synthetic Cl⁻-

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Voltage-controlled translocation through $\sqrt{2}$ $\sqrt{2}$ $\sqrt{2}$ $\sqrt{2}$ $\sqrt{2}$ $\sqrt{2}$ $\sqrt{2}$ Voltage-controlled translocation through $\sqrt{2}$ 11 11

S.-P. Zheng, J.-J. Jiang, A. van der Lee, with the simultaneously regulated by pH is the 14 Channel Regulated by pH 18 18 chloride channels in bilayer membranes 13 13 simultaneously regulated by pH is demonstrated. This voltage/pH regulated 15 15 MHz and 1 channel system represents an unexplored 16 16 alternative for ion-pumping along artifi-

17 A Voltage-Responsive Synthetic Cl⁻-

17 cial ion-channels.

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Dr. Shao-Ping Zheng

 $\frac{42}{42}$ Dr. Ji-Jun Jiang http://orcid.org/0000-0001-9483-6033

43 Dr. 31 July 2001 (19. 100 Color 2001 - 103 Color 2002)
Dr. Arie van der Lee http://orcid.org/0000-0002-4567-1831

 $\frac{44}{45}$ Dr. Mihail Barboiu http://orcid.org/0000-0003-0042-9483 45 $21.$ $32.$ 45

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