THE ION CHANNEL FactsBook

INTRACELLULAR LIGAND-GATED CHANNELS

Edward C. Conley

AP
FactsBook Series

THE ION CHANNEL *FactsBook* II

Intracellular Ligand-Gated Channels

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Intracellular Ligand-Gated Channels

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Cumulative table of contents for Volumes I to IV

Contents
Cumulative table of contents for Volumes I to IV (entry 01)
Acknowledgements
Introduction and layout of entries (entry 02)
How to use *The Ion Channel FactsBook*
Guide to the placement criteria for each field
Abbreviations (entry 03)

VOLUME I EXTRACELLULAR LIGAND-GATED CHANNELS

***ELG Key facts* (entry 04)**
Extracellular ligand-gated receptor–channels – key facts

***ELG CAT 5-HT$_3$* (entry 05)**
Extracellular 5-hydroxytryptamine-gated integral receptor-channels

***ELG CAT ATP* (entry 06)**
Extracellular ATP-gated receptor-channels ($P_{2X}R$)

***ELG CAT GLU AMPA/KAIN* (entry 07)**
AMPA / kainate-selective (non-NMDA) glutamate receptor-channels

***ELG CAT GLU NMDA* (entry 08)**
N-Methyl-D-aspartate (NMDA)-selective glutamate receptor–channels

***ELG CAT nAChR* (entry 09)**
Nicotinic acetylcholine-gated integral receptor–channels

***ELG Cl GABA$_A$* (entry 10)**
Inhibitory receptor-channels gated by extracellular gamma-aminobutyric acid

***ELG Cl GLY* (entry 11)**
Inhibitory receptor-channels gated by extracellular glycine

Feedback and access to the Cell-Signalling Network (entry 12)

Rubrics (entry 13)
Entry and field number rubrics

VOLUME II INTRACELLULAR LIGAND-GATED CHANNELS

***ILG Key facts* (entry 14)**
The intracellular ligand-gated channel group – key facts

***ILG Ca AA-LTC$_4$ [native]* (entry 15)**
Native Ca^{2+} channels gated by the arachidonic acid metabolite leukotriene C_4 *incorporating general properties of ion channel regulation by* **arachidonate metabolites**

***ILG Ca Ca InsP$_4$S [native]* (entry 16)**
Native Ca^{2+} channels sensitive to inositol 1,3,4,5-tetrakisphosphate ***(InsP$_4$)***

***ILG Ca Ca RyR-Caf* (entry 17)**
Caffeine-sensitive Ca^{2+}-release channels (ryanodine receptors, RyR)

***ILG Ca CSRC [native]* (entry 18)**
Candidate native intracellular-ligand-gated Ca^{2+}-store repletion channels

***ILG Ca InsP$_3$* (entry 19)**
Inositol 1,4,5-trisphosphate-sensitive Ca^{2+}-release channels ($InsP_3R$)

ILG CAT Ca [native] **(entry 20)**
Native calcium-activated non-selective cation channels (NS_{Ca})

ILG (CAT) cAMP **(entry 21)**
Cation channels activated in situ by intracellular cAMP

ILG CAT cGMP **(entry 22)**
Cation channels activated in situ by intracellular cGMP

ILG Cl ABC-CF **(entry 23)**
ATP-binding and phosphorylation-dependent Cl^- channels (CFTR)

ILG Cl ABC-MDR/PG **(entry 24)**
Volume-regulated Cl^- channels (multidrug-resistance P-glycoprotein)

ILG Cl Ca [native] **(entry 25)**
Native calcium-activated chloride channels (Cl_{Ca})

ILG K AA [native] **(entry 26)**
Native potassium channels activated by arachidonic acid (K_{AA}) incorporating *general properties* of ion channel regulation by *free fatty acids*

ILG K Ca **(entry 27)**
Intracellular calcium-activated K^+ channels (K_{Ca})

ILG K Na [native] **(entry 28)**
Native intracellular sodium-activated K^+ channels (K_{Na})

VOLUME III INWARD RECTIFIER AND INTERCELLULAR CHANNELS

INR K Key facts **(entry 29)**
Inwardly-rectifying K^+ channels – key facts

INR K ATP-i [native] **(entry 30)**
Properties of intracellular ATP-inhibited K^+ channels in native cells

INR K G/ACh [native] **(entry 31)**
Properties of muscarinic-activated K^+ channels underlying I_{KACh} in native cells

INR K [native] **(entry 32)**
Properties of 'classical' inward rectifyer K^+ channels in native cells (excluding types covered in entries 30 & 31)

INR K [subunits] **(entry 33)**
Comparative properties of protein subunits forming inwardly-rectifying K^+ channels (*heterologously-expressed* cDNAs of the K_{IR} family)

INR (K/Na) I_{fhQ} [native] **(entry 34)**
Hyperpolarization-activated cation channels underlying the inward currents i_f, i_h, i_Q

JUN [connexins] **(entry 35)**
Intercellular gap junction channels formed by connexin proteins

MEC [mechanosensitive] **(entry 36)**
Survey of ion channel types activated by mechanical stimuli

MIT [mitochondrial] **(entry 37)**
Survey of ion channel types expressed in mitochondrial membranes

NUC [nuclear] **(entry 38)**
Survey of ion channel types expressed in nuclear membranes

OSM [aquaporins] **(entry 39)**
The vertebrate aquaporin (water channel) family

SYN [vesicular] **(entry 40)**
Channel-forming proteins expressed in synaptic vesicle membranes (synaptophysin)

VOLUME IV VOLTAGE-GATED CHANNELS

VLG Key facts **(entry 41)**
Voltage-gated channels – key facts

VLG Ca **(entry 42)**
Voltage-gated Ca^{2+} channels

VLG Cl **(entry 43)**
Voltage-gated chloride channels

VLG K A-T **(entry 44)**
Properties of native 'A-type' (transient outward) potassium channels in native cells

VLG K DR **(entry 45)**
Properties of native delayed rectifier potassium channels in native cells

VLG K eag/elk/erg **(entry 46)**
K^+ channels related to *Drosophila* gene subfamilies *eag,elk,erg*

VLG K Kv-beta **(entry 47)**
Beta subunits *associated with Kv (alpha subunit) channel complexes*

VLG K Kv1-Shak **(entry 48)**
Vertebrate K^+ channel subunits related to *Drosophila Shaker* (Kv subfamily 1) *incorporating general features of Kv channel expression in heterologous cells*

VLG K Kv2-Shab **(entry 49)**
Vertebrate K^+ channel subunits related to *Drosophila Shab* (Kv subfamily 2)

VLG K Kv3-Shaw **(entry 50)**
Vertebrate K^+ channel subunits related to *Drosophila Shaw* (Kv subfamily 3)

VLG K Kv4-Shal **(entry 51)**
Vertebrate K^+ channel subunits related to *Drosophila Shal* (Kv subfamily 4)

VLG K Kvx (Kv5.1/Kv6.1) **(entry 52)**
Features of the 'non-expressible' cDNAs IK8 and K13

VLG K M-i [native] **(entry 53)**
Properties of native 'muscarinic-inhibited' K^+ channels underlying I_M

VLG (K) minK **(entry 54)**
'Minimal' protein subunits inducing 'slow-activating' voltage-gated K^+ currents

VLG Na **(entry 55)**
Voltage-gated Na^+ channels

ION CHANNEL RESOURCES (for access, see Vol. IV)

Resource A **(entry 56)**
G protein-linked receptors regulating ion channel activities *(alphabetical listing)*

Resource B **(entry 57)**
'Generalized' electrical effects of endogeneous receptor agonists

Resource C **(entry 58)**
Compounds and proteins used in ion channel research

Resource D **(entry 59)**
'Diagnostic' tests

Resource E **(entry 60)**
Ion channel book references (sorted by year of publication)

Resource F **(entry 61)**
Supplementary ion channel reviews (listed by subject)

***Resource G* (entry 62)**
Reported 'consensus sites' and 'motifs' in primary sequences of ion channels

***Resource H* (entry 63)**
Listings of cell types

***Resource I* (entry 64)**
Framework of cell-signalling molecule types (preliminary listing)

***Resource J* (entry 65)**
Search criteria & CSN development

***Resource K* (entry 66)**
Framework for a multidisciplinary glossary

Cumulative page index (for volumes I–IV)

Feedback: Comments and suggestions regarding the scope, arrangement and other matters relating to the coverage/contents can be sent to the e-mail feedback file CSN-01@le.ac.uk. *(see field 57 of most entries for further details)*

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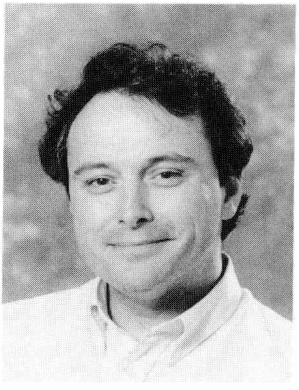

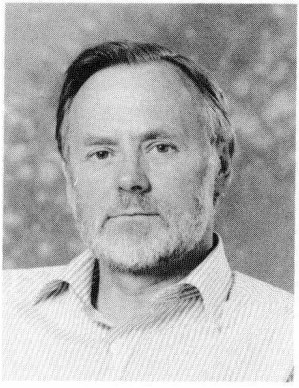

Left: *Edward Conley*, Right: *William Brammar*

Introduction & layout of entries

Edward C. Conley

Entry 02 resumé

The Ion Channels FactsBook is intended to provide a 'summary of molecular properties' for all known types of ion channel protein in a cross-referenced and 'computer-updatable' format. Today, the subject of ion channel biology is an extraordinarily complex one, linking several disciplines and technologies, each adding its own contribution to the knowledge base. This diversity of approaches has left a need for accessible information sources, especially for those reading outside their own field. By presenting 'facts' within a **systematic framework**, the *FactsBook* aims to provide a 'logical place to look' for specific information when the need arises. For students and researchers entering the field, the weight of the existing literature, and the rate of new discoveries, makes it difficult to gain an overview. For these readers, *The Ion Channels FactsBook* is written as a **directory**, designed to identify similarities and differences between ion channel types, while being able to accommodate new types of data within the framework. The main advantages of a systematic format is that it can speed up identification of **functional links** between any 'facts' already in the database and maybe provide a *raison d'être* for specific experiments where information is not known. Although such 'facts' may not go out-of-date, interpretations based on them may change considerably in the light of additional, more direct evidence. This is particularly true for the explosion of new information that is occurring as a direct consequence of the **molecular cloning of ion channel genes**. It can be anticipated that many more ion channel genes will be cloned in the near future, and it is also likely that their functional diversity will continue to exceed expectations based on pharmacological or physiological criteria alone.

An emphasis on properties emergent from ion channel molecular functions

Understanding how the interplay of currents through many specific ion channel molecules determines complex electrophysiological behaviour of cells remains a significant scientific challenge. The approach of the *FactsBook* is to associate and relate this complex cell phenotypic behaviour (e.g. its physiology and pharmacology) to ion channel **gene expression-control** wherever possible *even where the specific gene has not yet been cloned.* Thus the ion channel *molecule* becomes the **central organizer**, and accordingly arbitrates whether information or topics are included, emphasized, sketched-over or excluded. In keeping with this, ion channel characteristics are described in relation to known structural or genetic features wherever possible (or where they are ultimately **molecular characteristics**). Invariably, this relies on the availability of sequence data for a given channel or group of channels. However, a number of channel types exist which have not yet been sequenced, or display characteristics in the **native form** which are not precisely matched by existing clones expressed in heterologous cells (or are otherwise ambiguously classified). To accommodate these channel types, summaries of characteristics are included in the **standard entry field format**, with inappropriate fieldnames omitted. Thus the present 'working arrangement' of entries and fields is broad enough to include both the 'cloned' and 'uncloned' channel types, but in due course will be gradually supplanted by a comprehensive classification based on gene locus, structure, and relatedness of primary sequences. In all cases, the scope of the *FactsBook* entries is limited to those proteins forming (or predicted to form) membrane-bound, **integral ionic channels**

by folding and association of their primary protein sequences. Activation or suppression of the channel current by a specified ligand or voltage step is generally included as part of the channel description or name *(see below)*. Thus an emphasis is made throughout the book on **intrinsic features** of channel molecule itself and not on those of separately encoded, co-expressed proteins. In the present edition, there is a bias towards descriptions of **vertebrate ion channels** as they express the full range of channel types which resemble characteristics found in most eukaryotes.

Anticipated development of the dataset – Integration of functional information around molecular types

Further understanding of complex cellular electrical and pharmacological behaviour will not come from a mere catalogue of protein properties alone. This book therefore begins a process of specific **cross-referencing** of molecular properties within a **functional framework**. This process can be extended to the interrelationships of ion channels and other classes of **cell-signalling molecules** and *their* functional properties. Retaining protein molecules (i.e. gene products) as 'fundamental units of classification' should also provide a framework for understanding complex physiological behaviour resulting from co-expressed *sets* of proteins. Significantly, many **pathophysiological phenotypes** can also be linked to selective molecular 'dysfunction' within this type of framework. Finally, the anticipated growth of raw sequence information from the **human genome project** may reveal hitherto unexpected classes and subtypes of cell-signalling components – in this case the task then will be to integrate these into what is already known *(see also description of Field number 06: Subtype classifications and Field number 05: Gene family)*.

The Cell-Signalling Network (CSN)

From the foregoing discussion, it can be seen that establishment and consolidation of an integrated '**consensus database**' for the many diverse classes of cell signalling molecules (including, for example, receptors, G proteins, ion channels, ion pumps, etc.) remains a worthwhile goal. Such a resource would provide a focus for identifying unresolved issues and may avoid unnecessary duplication of research effort. Work has begun on a prototype **cell-signalling molecule database** co-operatively maintained and supported by contributions from specialist groups world-wide: The ***Cell-Signalling Network (CSN)*** operating from mid-1996 under the **World Wide Web**† of the Internet† has been designed to disseminate **consensus properties** of a wide range of molecules involved in cell signal transduction. While it may take some time (and much good-will) to establish a comprehensive network, the many advantages of such a co-operative structure are already apparent. Immediately, these include an 'open' mechanism for **consolidation** and **verification** of the dataset, so that it holds a 'consensus' or 'validated' set of information about what is known about each molecule and practical considerations such as **nomenclature recommendations** (see, for example, the IUPHAR nomenclature sections under the CSN 'home page').

The CSN also allows **unlimited cross-referencing** by pointing to related information sets, even where these are held in multiple centres around the world. **On-line** support for technical terms (**glossary items**, indicated by **dagger symbols** (†) throughout the

text) and reference to explanatory **appendices** (e.g. on associated signalling components such as G protein†-linked receptors†) are already supported for use with this book. Eventually, benefits could include (for instance) direct 'look-up' of graphical resources for protein structure, *in situ* and developmental **gene expression atlases**†, interactive **molecular models** for structure/function analysis, DNA/protein sequences linked to feature tables, **gene mapping** resources and other pictorial data. These developments (not all are presently supported) will use **interactive electronic media** for efficient browsing and maintenance. *For a brief account of the Cell-Signalling Network, see Feedback & CSN access, entry 12. For a full specification, see Resource J – Search criteria & CSN development, entry 65.*

HOW TO USE *THE ION CHANNEL FACTSBOOK*

Common formats within the entries

A proposed organizational hierarchy for information about ion channel molecules

Information on named channel types is grouped in **entries** under common headings which repeat in a fixed order – e.g. for ion channel molecules which have been sequenced, there are broad **sections** entitled NOMENCLATURES, EXPRESSION, SEQUENCE ANALYSES, STRUCTURE & FUNCTIONS, ELECTROPHYSIOLOGY, PHARMACOLOGY, INFORMATION RETRIEVAL and REFERENCES, in that order. Within each section, related **fieldnames** are listed, always in **alphabetical order** and indexed by a **field number** *(see below)*, which makes electronic cross-referencing and 'manual' comparisons easier.

While the sections and fields are *not* rigid categories, an attempt has been made to remain consistent, so that corresponding information for two different channels can be looked up and compared directly. If a field does not appear, either the information was not known or was not found during the compilation period. Pertinent information which has been published but is absent from entries would be gratefully received and will be added to the 'entry updates' sections within the CSN *(see Feedback & CSN access, entry 12)*. Establishment of this 'field' format has been designed so that every available 'fact' should have its logical 'place'. In the future, this arrangement may help to establish 'universally accepted' or '**consensus**' properties of any given ion channel or other cell-signalling molecule. This **validation** process critically depends on user feedback to contributing authors. The CSN *(above)* establishes an efficient electronic mechanism to do this, for continual refinement of entry contents.

Independent presentation of 'facts' and conventions for cross-referencing

The *FactsBook* departs from a traditional review format by presenting its information in related groups, each under a broader heading. *Entries are not designed or intended to be read 'from beginning to end', but each 'fact' is presented independently under the* ***most pertinent fieldname***. Independent citation of 'facts' may sometimes result in some **repetition** (redundancy) of general

principles between fields, but if this is the case some effort has been made to 're-phrase' these for clarity (suggested improvements for presentation of any 'fact' are welcome – *see Field number 57: Feedback*).

For readers unfamiliar with the more general aspects of ion channel biology, some introductory information applicable to whole groups of ion channel molecules is needed, and this is incorporated into the **'key facts' sections** preceding the relevant set of entries. These sections, coupled with the **'electronically updated' glossary items** (available on-line, and indicated by the dagger† symbol, *see below*) provide a basic overview of principles associated with detailed information in the main entries of the book.

Extensive **cross-referencing** is a feature of the book. For example, cross-references between fields of the *same* entry are of the format *(see Fieldname, xx-yy)*. Cross-references between fields of *different* channel type entries are generally of the format *see fieldname under SORTCODE, xx-yy;* for example – *see mRNA distribution, under ELG Cl GABA$_A$, 10-13*. This **alphabetical 'sortcode'** and **numerical 'entry numbers'** (printed in the **header** to each page) are simply devices to make cross-referencing more compact and to arrange the entries in an approximate **running order** based on **physiological features** such as mode of gating†, ionic selectivity†, and agonist† specificity. A 'sort order' based on physiological features was judged to be more intuitive for a wider readership than one based on gene structure alone, and enables 'cloned' and 'uncloned' ion channel types to be listed together. The use and criteria for sortcode designations are described under the subheading *Derivation of the sortcode (see Field number 02: Category (sortcode))*. Entry 'running order' is mainly of importance in book-form publications. **New entries** (or mergers/subdivisions between existing entries) will use serial entry numbers as 'electronic pointers' to appropriate files.

Cross-references are frequently made to an on-line index of **glossary items** by **dagger symbols**† wherever they might assist someone with technical terms and concepts *when reading outside their own field.* The glossary is designed to be used side-by-side with the *FactsBook* entries and is accessible in updated form over the Internet†/World Wide Web† with suitable browsing† software *(for details, see Feedback & CSN access, entry 12)*.

Contextual markers and styles employed within the entries

Throughout the books, a **six-figure index number** (xx-yy-zz, e.g. 19-44-01:) separates groups of facts about different aspects of the channel molecule, and carries information about **channel type/entry number** (e.g. **19-** ~ $InsP_3$ receptor–channels), **information type/field number** (e.g. **-44-**, *Channel modulation*) and **running paragraph number (datatype)** (e.g. **-01**). This simple 'punctate' style has been adopted for maximum flexibility of **updating** (both error-correction and consolidation with new information), **cross-referencing** and **multi-authoring**. The CSN specification *(see entry 65)* includes longer term plans to structure field-based information into convenient **data-types** which will be indexed by a zz numerical designation.

Italicized subheadings are employed to organize the facts into related topics where a field has a lot of information associated with it. Specific illustrated points or features within a field are referenced to adjacent figures. Usage of abbreviations and common

symbols are defined in context and/or within the main **abbreviations index** at the front of each book. Abbreviated **chemical names** and those of proprietary pharmaceutical compounds are listed within the electronically updated *Resource C – Compounds & proteins*, also available via the 'home page' of the *Cell-Signalling Network*.

Generally, highlighting of related **subtopics** emergent from the molecular properties ('facts') associated with the ion channel under description are indicated within a field by **lettering in bold**. All subtopics are cross-referenced by means of a large **cumulative subject index** (entry 66), which can permit retrieval of information by topic *without requiring prior knowledge of ion channel properties*. Throughout the main text, *italics* draw attention to special cases, caveats, hypotheses and exceptions. The '*Note: '* prefix has been used to indicate **supplemental** or comparative information of significance to the quoted data in context.

Special considerations for integrating properties derived from 'cloned' and 'native' channels

While a certain amount of introductory material is given to set the context, the emphasis on **molecular properties** means the treatment of many important biological processes or phenomena is reduced to a bare outline. References given in the *Related sources and reviews* field and the electronically updated *Resource F – Supplementary ion channel reviews* accessible via the CSN *(see Feedback & CSN access, entry 12)* are intended to address this imbalance.

For summaries of key molecular features, a central channel '**protein domain topography model**' is presented. Individual features that are illustrated on the protein domain topography model are identified within the text by the symbol **[PDTM]**.

Wherever **molecular subtype-specific data** are quoted (such as the particular behaviour of a ion channel gene family† member or isoform†) a convention of using the underlined trivial or systematic name as a prefix has been adopted – e.g. mIRK1: ; RCK1: ; Kv3.1: etc.

GUIDE TO THE PLACEMENT CRITERIA FOR EACH FIELD

Criteria for NOMENCLATURES sections

This section should bring together for comparison present and previous names of ion channels or currents, with brief distinctions between similar terms. Where ***systematic names*** *have already been suggested or adopted by published convention, they should be included and used in parallel to trivial names.*

Field number 01: ***Abstract/general description:*** This field should provide a summary of the most important functional characteristics associated with the channel type.

Field number 02: ***Category (sortcode):*** The **alphabetical 'sortcode'** should be used for providing a logical **running order** for the individual entries which make up the book. It is *not* intended to be a rigorous channel classification, which is under discussion,

but rather a **practical index** for finding and cross-referencing information, in conjunction with the **six-figure index number** *(see above)*. The *Category (sortcode)* field also lists a designated **electronic retrieval code** (unique embedded identifier or **UEI**) for 'tagging' of new articles of relevance to the contents of the entry. For further details on the use and implementation of UEIs, *see the description for Resource J* (in this entry) and for a full description, *see Resource J – Search criteria & CSN development, entry 65.*

Derivation of the sortcode: Although we do not yet have a complete knowledge of all ion channel primary† structures, knowledge of ion channel gene family† and superfamily† structure allows a *working* **sort order** to be established. To take an example, the extracellular ligand-gated (ELG) receptor–channels share many structural features, which reflects the likely duplication and divergent evolution of an ancestral gene. The present-day forms of such channels reflect the changes that have occurred through adaptive radiation† of the ancestral type, particularly for gating† mechanism and ionic selectivity† determinants. Thus, the **entry running order** (alphabetical, via the sortcode) of the *FactsBook* entries should depend primarily on these two features. The sortcode therefore consists of several groups of letters, each denoting a characteristic of the channel molecule: Entries are sorted first on the principal means for **channel gating**† (first three letters), whether this is by an extracellular ligand† (ELG), small intracellular ligand† (ILG) or transmembrane voltage (VLG). For convenience, the ILG entries also include certain channels which are obligately dependent on *both* ligand binding *and* hydrolysis for their activation – e.g. channels of the ATP-binding cassette (ABC) superfamily. Other channel types may be subject to direct mechanical gating (MEC) or sensitive to changes in osmolarity (OSM) – *see the Cumulative tables of contents* and the first page of each entry for descriptions and scope. Due to their unusual gating characteristics, a separate category (INR) has been created for **inward rectifier-type channels.**

The second sort (the next three letters of the sortcode) should be on the basis of the principal **permeant ions**, and may therefore indicate high selectivity for **single ions** (e.g. Ca, Cl, K, Na) or **multiple ions** of a specified charge (e.g. cations – CAT). Indefinite **sortcode extensions** can be assigned to the sortcode if it is necessary to distinguish similar but separately encoded groups of channels *(e.g. compare ELG Cl $GABA_A$, entry 10 and ELG Cl GLY, entry 11).*

Field number 03: ***Channel designation:*** This field should contain a shorthand designation for the ion channel molecule – mostly of the form X_Y or $X_{(Y)}$ where X denotes the major **ionic permeabilities**† (e.g. K, Ca, cation) and Y denotes the principal **mechanism of gating**† *where this acts directly on the channel molecule itself* (e.g. cGMP, voltage, calcium, etc.). Otherwise, this field contains a shorthand designation for the channel which is used in the entry itself.

Field number 04: ***Current designation:*** This field should contain a shorthand designation for ionic currents conducted by the channel molecule, which is mostly of the form $I_{X(Y)}$, $I_{X,Y}$ or $I_{X\text{-}Y}$ where X and Y are defined as above.

Field number 05: ***Gene family:*** This field should indicate the known **molecular relationships** to other ion channels or groups of ion channels at the level of

amino acid primary sequence homology†, within gene families† or gene superfamilies†. Where **multiple channel subunits** are encoded by separate genes, a summary of their principal features should be tabulated for comparison. Where the gene family is particularly large, or cannot be easily described by functional variation, a **gene family tree**† derived by a **primary sequence alignment algorithm**† *(see Resource D – 'Diagnostic' tests, entry 59)* may be included as a figure in this field.

Field number 06: *Subtype classifications:* This field should include supplementary information about any schemes of classification that have been suggested in the literature. Generally, the most robust schemes are those based on complete knowledge of **gene family**† **relationships** *(see above)* and this method can identify similarities that are not easily discernible by pharmacological or electrophysiological criteria alone – see, for example, the entries *JUN (connexins), entry 35*, and *INR K (subunits), entry 33*. Note, however, that some native† channel types are more conveniently 'classified' by functional or cell-type expression parameters which take into account interactions of channels with other co-expressed proteins (see, for example, discussion pertaining to the cyclic nucleotide-gated (CNG-) channel family in the entries *ILG Key facts, entry 14*, *ILG CAT cAMP, entry 21*, and *ILG CAT cGMP, entry 22*. Debate on the 'best' or 'most appropriate' channel classification schemes is likely to continue for some time, and it is reasonable to suppose that alternative subtype classifications may be applied and used by different workers for different purposes.

Since the 'running order' of the *FactsBook* categories depends on inherent molecular properties of channel cDNAs†, genes† or the expressed proteins, future editions will gradually move to classification on the basis of **separable gene loci**†. Thus multiple channel protein variants resulting from processes of **alternative RNA splicing**† but encoded by a **single gene locus**† will only ever warrant one 'channel-type' entry (e.g. see BK_{Ca} variants under *ILG K Ca, entry 27*). Distinct proteins resulting from transcription† of **separable gene loci**, for example in the case of different gene family members, will (ultimately) warrant separate entries. For the time being, there is insufficient knowledge about the precise phenotypic† roles of many 'separable' gene family members to justify separate entries (as in the case of the *VLG K Kv* series entries).

Classification by **gene locus designation** *(see Field number 18: Chromosomal location)* can encompass all structural and functional variation, while being 'compatible' with efforts directed to identifying phenotypic and pathophysiological† roles of individual gene products (e.g. by gene-knockout†, locus replacement† or disease-linked gene mapping† procedures – *see Resource D – 'Diagnostic' tests, entry 59*). Subtype classifications based on gene locus control can also incorporate the marked developmental changes which pertain to many ion channel genes *(see Field number 11: Developmental regulation)* and can be implemented when the 'logic' underlying **gene expression-control**† for each family member is fully appreciated. A 'genome-based' classification of *FactsBook* entries may also help comprehend and integrate **equivalent information** based for other ('non-channel') cell-signalling molecules *(see Resources G, H and I, entries 62, 63 and 64)*.