# Regenerative Medicine

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The audience for *Regenerative Medicine* consists of clinicians, research scientists, decision-makers and a range of professionals in the healthcare and scientific community. Authors should bear in mind the multidisciplinary status of the readership when writing the article. *Regenerative Medicine* articles have been engineered specifically for the time-constrained professional. The structure is designed to draw the reader's attention directly to the information they require. Our author guidelines are given below.

## Article format

Specific requirements for each article type are given below – these should be followed closely. It is recognized however that the structure of individual articles must reflect the topic.

### *Title page*

The title page of all article types should include the following information:

- Title (not more than 120 characters)
- Authors' names, including first name in full (no more than six authors per review)
- Authors' affiliations, including phone/fax/e-mail
- Summary – not more than 150 words this should not be an abstract but merely a scene-setting summary outlining the article scope and briefly putting it in context. The role of the summary is to draw in the interested casual browser.
- Keywords – up to 10 keywords (including therapeutic area, mechanism(s) of action etc.) plus names of drugs and compounds mentioned in the text.

## Article structure

### *Introduction*

The introduction should seek to define the area under review and relate it to potential therapeutic applications.

### *Body of article*

This section should be divided according to the specific approaches reviewed within.

### *Conclusion/Expert Commentary*

A summary of the data and concepts presented in the review, including your own personal assessment of the subject under review.

### *Future Perspective*

The author is challenged to include speculative viewpoint on how the field will have evolved 5–10 years from the point at which the review was written.

### *Executive Summary*

Executive summary comprised by a series of bulleted statements (typically 8–10) representing key conclusions, unresolved issues and points for emphasis of work in future (see page 5 for an example).

**Three features in particular contribute to the unique value of *Regenerative Medicine* articles: Future Persepctive, Highlights and the use of figures, tables and boxes.**

- **Future Perspective:** Authors are challenged to include a speculative viewpoint on how the field will evolve over the next 5–10 years from the point at which the review was written.
- **Executive Summary:** A summary of the authors' main points (bulleted) is very useful for time-constrained readers requiring a rapidly accessible overview (see page 5 for an example).
- **Use of figures, tables and boxes:** Summary tables and/or figures are very useful. The author should include illustrations and provide at-a-glance understanding with tables to condense and illustrate the information they wish to convey. Commentary that augments an article and could be viewed as 'stand-alone' should be included in a separate box. An example would be a summary of a particular trial or trial series, a case study summary or a series of terms explained.

future medicine

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#### *References*

References should not include data on file or personal communication (mention in text).

## Article types

### *Original research articles*

The organization of original research papers is as follows:

- Abstract (around 300 words or less), followed by 6 to 8 key words for indexing
- Introduction
- Patients and methods/Materials and methods
- Results
- Discussion
- Conclusions
- 'Summary points' – 8–10 bullet point sentences highlighting the key findings and conclusions of the research study
- Acknowledegments
- References

### *Review articles*

Each article should concentrate on the most recent developments in the field and should aim for concise presentation of the relevant information. These articles aim to summarize current therapeutic practice, highlighting recent significant advances in research, ongoing challenges and unmet needs. Authors should strive for brevity and clarity – articles should be between 4000–8000 words. The final structure of the review will, of course, depend on the title/focus but wherever possible, the following sections should be included.

### *Perspectives*

These should more speculative and very forward looking, even visionary. They also offer the author the opportunity to present criticism or address controversy. Authors of perspectives are encouraged to be highly opinionated. The intention is very much that perspectives should represent a personal perspective. Referees will be briefed to review these articles for quality and relevance of argument only. They will not necessarily be expected to agree with the authors' sentiments. As for regular reviews, the article should include an Executive Summary.

### *Priority paper evalutions*

*Regenerative Medicine* Priority Paper Evaluations review significant, recently published articles carefully selected and assessed by specialists in the field. The primary research detailed in the chosen paper is discussed with the aim of keeping readers informed of the most promising discoveries/breakthroughs relevant to the field through review and comment from experts. Priority Paper Evaluations are intended to extend and expand on the information presented, putting it in context and explaining why it is of importance.

#### *Scope*

The ideal article will provide both a critical evaluation and the author's opinion on the quality and novelty of the information disclosed.

#### *Length*

1000–1500 words (not including tables, figures and references).
Every Paper Evaluation must contain:

#### *Title*

Should be concise but informative and contain no brand names.

#### *Authors' names and addresses*

Including telephone number, fax number and e-mail address and denoting an author for correspondence.

#### *Abstract*

A short abstract, ~ 100 words, bringing together the main points under discussion.

#### *Keywords*

A brief list of keywords to assist indexers in cross-referencing.

#### *Introduction*

The paper under discussion must be introduced and referenced as Reference [1]. The scientific and/or commercial rationale behind the paper is presented, giving some perspective on the information disclosed, placing it in context with previous research in the same area and indicating the relative importance of this new work. Authors may highlight other contemporary papers that have relevance to the main paper; these may support or conflict with the results. It is essential that a critical stand is taken when writing.

#### *Results from the paper*

Comment upon the extent and quality of the experimental models used and how elegantly the experiments were performed.

*Significance of the results*

Comment upon the claims made in the authors' discussion section. Do the results look promising? How is this paper going to change research in the field? Or is the paper the evidence for a significance theory?

*Your 'Perspective'*

An essential section that should offer your opinion on the developments discussed in the article – is the paper going to affect future research? Is this avenue of research likely to become exciting and possibly yield new drug targets and affect pharmaceutical research? Comparative assessment is encouraged.

*Technology Reports*

These articles will focus on a specific aspect of performance of a particular technology or approach. This could address one issue among those comprising a complete overview of a new technology. As for regular reviews, the article should include an Executive Summary and Future Perspective.

## Manuscript preparation

*Extent*

Manuscripts should be up to 4000 words in length with a target of no more than 80 references.

*Spacing & headings*

Please use double line spacing throughout the manuscript. Four levels of subheading should be used to divide the text: LEVEL 1, Level 2, *Level 3*, Level 4

*Abbreviations*

Abbreviations should be defined on their first appearance; commonly used abbreviations need not be defined. Use SI units or quote SI equivalents where possible. To indicate atom positions in a molecule, use the convention C-1, C-2 etc.

*Spelling*

US-preferred spelling will be used in the finished publication (e.g., leukemia, not leukaemia).

## Companies & compounds

Companies are treated as single entities requiring a verb in the third person singular, e.g. Glaxo is developing an AII antagonist. When referring to a lead compound (or compounds claimed in patents) for the first time, please ensure that the name of the relevant company is given in the text.

## References & reference annotations

Authors should focus on recent papers and papers older than 5 years should not be included except for an over-riding purpose.

NB Papers or patents of particular interest should be identified using one or two asterisk symbols (* = of interest, ** = of considerable interest) and annotated with a brief sentence explaining why the reference is considered to be of interest.

References should be denoted numerically and in sequence in the text, using Arabic numerals placed in square brackets, i.e. [12]. List references in numerical order in the Reference list. If websites or patents are included, please use a separate numbering system for them, i.e. start numbering website references at [101] and patents at [201] to allow the reader to distinguish between websites/patents and primary literature references both in the text and in the bibliography. Please ensure that each reference applies to only one website.

*Format for reference citations*

Author's names should appear without full stops in their initials.

Quote first six authors' names. If there are more, then quote first three *et al.*

A colon follows authors' names.

Journal names in italics and abbreviated to standard format.

Volume number followed by a comma, not in bold.

Page number range separated by a hyphen and no spaces, followed by the year in brackets and then a full stop.

- Journal example
  Fantl JA, Cardozo L, McClish DK *et al.*: estrogen therapy in the management of urinary incontinence in postmenopausal women: a meta-analysis. First report of the Hormones and Urogenital Therapy Committee. *Obstet. Gynecol.* 83(1), 12–18 (1994).
- Book example
  De Groat WC, Booth AM, Yoshimura N: Neurophysiology of micturition and its modification in animal models of human disease. In: *The Autonomic Nervous System (Volume 6). Nervous Control of the Urogenital System*. Andrews WR (Ed.), Harwood Academic Publishers, London, UK, 227–289 (1993).
- Meeting abstracts example
  Smith AB, Jones CD: Recent progress in the therapy of diseases of the small bowel. Pro-

ceedings of the 13th International Symposium on Medicinal Chemistry. Atlanta, USA, MED197 (1994).

- Patent example
  Merck Frosst Canada, Inc. WO9714691 (1997).
  (Use the following formats for patent numbers issued by the World, US and European patent offices, respectively: WO1234567, US1234567, EP-123456-A)

### Illustrations

Please provide electronic copies if possible. If this is not possible, please ensure that camera-ready copy is of the highest resolution available.

Figures should be numbered consecutively according to the order in which they have been first cited in the text. Define in the legend all abbreviations that are used in the figure.

Figures and structures should be in separate files to the text. It is unnecessary to incorporate the figures into the body of the manuscript. If a figure has been published, acknowledge the original source and submit written permission from the copyright holder to reproduce the material. If payment is required for use of the figure, this should be covered by the author honorarium, unless otherwise agreed.

### Chemical structures

If possible, please submit structures drawn in ISIS Draw or Chemdraw format. However, chemical structures can be redrawn in-house. Please use the following conventions:

- Always indicate stereochemistry where necessary – use the wedge and hash bond convention for chiral centres and mark cis/trans bonds as such.
- Draw small peptides (up to five amino acids) in full; use amino acid abbreviations (Gly, Val, Leu etc.) for larger peptides.
- Refer to each structure with a number in the text; submit a separate file (i.e., not pasted throughout the text) containing these numbered structures in the original chemical drawing package that you used and as a hard copy.

### Electronic figure files

Please submit any other illustrations/schemes in an electronic format such as Illustator, CorelDraw, Powerpoint, Excel or as postscripted/encapsulated postscripted (.ps/.eps) files. Otherwise, please ensure camera-ready copy is of high resolution.

### Copyright

As the author of your manuscript, you are responsible for obtaining permissions to use material owned by others. Since the permission-seeking process can be remarkably time-consuming, it is wise to begin writing for permission as soon as possible. A template permission letter is available on request. Please send us photocopies of letters or forms granting you permission for the use of copyrighted material so that we can see that any special requirements with regard to wording and placement of credits are fulfilled. Keep the originals for your files. Authors of all articles accepted for publication will be asked to assign copyright when they receive proofs for approval.

### Submission

If possible, please submit manuscripts in MS Word format. However, we can convert most word-processing packages. Please use high (not double) density disks. Submission by e-mail is welcome (e-mail address below), although we will always need hard copies of manuscripts to check for formatting changes. We can also decode BinHex 4.0 encoded e-mails (Mac encoding system).

### Deadlines & peer-review

Please ensure that manuscripts are submitted on or before the agreed deadline. Please also provide an outline of your review not later than one month prior to the submission deadline. This will enable us to find a suitable referee in advance. Once the manuscript has been received in-house, it will be peer-reviewed (this usually takes up to two weeks). A further two weeks is then allowed for any revisions (suggested by the referee/Editor) to be made. If a manuscript requires authorization by your organization before submission, please remember to take this into account when working towards these deadlines.

### Conflict of interest

It is the responsibility of the authors to disclose any affiliation with any organization with a financial interest, direct or indirect, in the subject matter or materials discussed in the manuscript (such as consultancies, employment, expert testimony, honoraria, speakers bureaus, retainers, stock options or ownership) that may affect the conduct or reporting of the work submitted. If uncertain as to what might be consid-

ered a potential conflict of interest, authors should err on the side of full disclosure. Information about potential conflict of interest may be made available to reviewers and may be published with the manuscript at the discretion of the Editors.

Our reputation for author care, quality control through the publishing process and rapid, timely publication is unrivalled. Typically, from receipt of a first draft to publication takes only 8-12 weeks allowing 2 weeks each for peer-review and revision.

*Regenerative Medicine* expects manuscripts to conform to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (the Vancouver style; *N. Engl. J. Med.* 336, 309–315 [1997] or www.icmje.org).

### Contact details

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## Executive Summary

***Epidemiology***

- Following the recent widespread use of CD 117 immunohistochemistry in routine pathologic analysis, GIST real incidence remains to be defined. GIST occurs with the same frequency in both sexes. The median age at occurrence is 60 years (range 10 to 92 years). This tumor is most commonly found in the stomach (52%), followed by the small intestine (25%) and then the large intestine (11%) and esophagus (5%). Only about 7% of tumors arise outside the intestinal tract: in the omentum, mesentery and peritoneum.

***Clinical presentation***

- The clinical presentation of GIST varies. Small silent lesions are finding during surgery, radiological or endoscopic studies performed for other reasons. Larger lesions have symptoms correlated with their size. Some patients present with acute hemorrhage from tumor rupture and/or bowel obstruction, perforation, dysphagia, anorexia and fever.

***Pathology***

- 90–100% of GIST present unequivocal diffuse, and marked cytoplasmic positivity for the CD 117 antigen, an epitope of the KIT receptor, tyrosine kinase.
- 60–70% of GIST are positive for CD 34
- 30–40% of GIST, especially those of the small intestine, stain for smooth muscle actine (SMA).
- GIST rarely express desmin or S100, and are negative for neurofilaments and glial fibrillary acid proteins.

***Predictors of malignant behavior***

- The "benign versus malignant" terminology is being replaced by a more useful distinction, made on the basis of risk assessment. The most acceptable and easily applicable morphologic criteria for predicting tumor behavior are tumor size and mitotic rate.

***Molecular biology***

- The fundamental pathogenic feature of GIST is a mutation that constitutively activated KIT proteins without the KIT ligand, stem cell factor.
- The tyrosine kinase activity of KIT can be activated by mutations of different exons of the *c-KIT* gene.
- Exon 11 mutations, encoding the c-KIT juxtamembrane domain are found in 55 to 77% of cases.
- Exon 9 mutations, encoding a region located in the extracellular domain, are found in 3 to 18% of GIST.
- Exons 13 and 17 mutations, encoding the intracellular part of the receptor, are reported to be extremely rare.
- In some GIST, lacking KIT mutations, intragenic mutations in the platelet-derived growth factor receptor $\alpha$ were demonstrated.

***Cytogenic changes and mechanism of progression***

- More than 90% of GIST has multiple chromosomal abnormalities. Some studies revealed compelling correlations between the acquisition of chromosomal aberrations and aggressive clinicopathologic behavior.

***Treatment***

- STI-571 is an orally administered competitive inhibitor of ATP binding to the tyrosine kinase domain of receptors including KIT protein, ABL protein, BCR-ABL fusion protein and PDGFR. Until the advent of imatinib, there was no effective treatment for unresectable or metastatic GIST. In 2001, Imatinib was approved by FDA for the treatment of malignant metastatic and/or unresectable GIST at a recommended dose of 400-600 mg a day. Ongoing trials aim to analyze the impact of adjuvant and neo-adjuvant therapy with imatinib in GIST patients.

***Mechanism of resistance to imatinib mesylate***

- Little is known about the resistance mechanisms of imatinib mesylate in the treatment of GIST. Preliminary data on resistance to STI571 revealed four mechanisms of resistance due to: new KIT or PDGFRA mutations; gene amplification; activation of an alternate receptor tyrosine kinase protein; KIT or PDGFRA activation, in the absence of a secondary mutation, with pre-treatment mutations outside the juxtamembrane hotspot region.

***Other tyrosine kinase inhibitors***

- A number of novel tyrosine kinase inhibitors active against KIT are under examination in patients with GIST disease. Among these, SU011248 was recently analyzed in a phase I/II trial in 75 patients with metastatic GIST refractory or intolerant to imatinib with a 15% of objective response, and 39% of stabilization of disease.

***Regional lymphadenectomy should be avoided since it is of unproven value***

- Imatinib therapy can be evaluated in a different timing and setting before and after surgery. However the role of surgical removal of residual disease after STI571 therapy has yet to be defined and requires further research. Otherwise, patients who become refractory to imatinib therapy may be eligible for other treatments: enrollment in protocol studies with others tyrosine kinase inhibitors, dose escalation of imatinib therapy or palliative therapy, such as radiotherapy, hepatic artery embolization, surgical debulking and/or intraperitoneal chemotherapy.