Commonalities in the endocrinology of stem cell biology and organ regeneration

Neil A. Hanley

Title: Commonalities in the endocrinology of stem cell biology and organ regeneration

Author: Neil A. Hanley

PII: S0303-7207(08)00127-5
DOI: doi:10.1016/j.mce.2008.04.001
Reference: MCE 6852

To appear in: *Molecular and Cellular Endocrinology*

Please cite this article as: Hanley, N.A., Commonalities in the endocrinology of stem cell biology and organ regeneration, *Molecular and Cellular Endocrinology* (2007), doi:10.1016/j.mce.2008.04.001

Commonalities in the endocrinology of stem cell biology and organ regeneration

Neil A Hanley

Centre for Human Development, Stem Cells & Regeneration; Human Genetics Division, University of Southampton, Southampton, UK.

***Corresponding author:**

Professor Neil A Hanley

Human Genetics Division,

Duthie Building, Mailpoint 808,

Southampton General Hospital, Tremona Road, Southampton, SO16 6YD, UK

Email: n.a.hanley@soton.ac.uk

Key Words: stem cell, progenitor cell, niche, microenvironment, organ, regeneration, tissue engineering, regenerative medicine

Abbreviations:

PTH, parathyroid hormone; HSC, haematopoietic stem cell; IGF, insulin-like growth factor; PTHrP, PTH related peptide; FGF, fibroblast growth factor; ESC, embryonic stem cell; GLP, glucagon-like peptide; T3, triiodothyronine; TR, thyroid hormone receptor; SHH, sonic hedgehog; BMP, bone morphogenic protein; MMP, matrix metalloproteinase; IGFBP, IGF binding protein; ER, estrogen receptor; GFP, green fluorescent protein; MSC, mesenchymal stem cell; SSC, spermatogonial stem cell; GCT, germ cell tumour; GDNF, glial cell line-derived neurotrophic factor; CIS, carcinoma-in-situ; EC, embryonal carcinoma; NPY, neuropeptide Y

'If it is not broken, do not try to fix it' is an adage that lauds the occasional virtue of inactivity. However, for most, if not all, of the human body's organs and tissues there is no such rest. All of the two hundred plus different cell-types within the human body constantly require careful attention to maintain optimal function. The longevity of our lives, far greater than the lifespan of most single cells, brings with it a requirement for continual tissue and organ regeneration, where cell loss is perfectly matched by cell replacement; continual 'breaking' that necessitates 'fixing' on a day-to-day, month-to-month and year-to-year basis. This issue of *Molecular & Cellular Endocrinology* examines the mechanisms underlying this process for a range of organs, both in health and disease coupled to the potential for selected cell replacement therapies.

The project set out with the goal of bringing together a range of articles examining the role of hormones and growth factors on stem or progenitor cells and their progeny in endocrine organs and other hormone-relevant sites (Table 1). The result is ten articles (Berry et al., 2008; Gargett et al., 2008; Garrett and Emerson, 2008; Gray, 2008; Hanley et al., 2008; Hoffman, 2008; Ishizuya-Oka and Shi, 2008; Kristensen et al., 2008; Paus et al., 2008; Rowland and Brubaker, 2008) that should be considered alongside a previous review in *Molecular & Cellular Endocrinology* on the regeneration of the adrenal cortex from resident stem cells (Kim and Hammer, 2007). To complement these in vivo paradigms, three examples are included here of current in vitro stem cell work aiming to generate terminally differentiated cell-types for clinical therapy (Best et al., 2008; Moore et al., 2008; Tare et al., 2008): an endocrine twist on cell therapy meets regenerative biology. The outcome underlines mechanistic themes with the potential for new research driven by extrapolation across otherwise distinct locations. One emergent thread running through many of the articles is the critical importance of microenvironment—the 'niche', comprised of stem or progenitor cells in vascularised biological matrices that respond selectively to a range of intercellular signals depending upon, amongst other factors, cell receptor expression. Correct assembly of the niche permits healthy organs and tissues that

continually regenerate without scarring, and offers the blueprint for ex vivo tissue engineering. Other articles describe dysplastic or aberrant construction as a potentially causative factor in a range of disorders and diseases from epilepsy to cancer.

In some locations, such as the central nervous system (CNS) (Gray, 2008) and pancreas (Hanley et al., 2008), the presence of clearly defined adult stem cells or progenitors remains contentious. However, for these organs it is still possible to discern microenvironments, either in situ or once cells have been taken in vitro, where a regenerative capacity seems feasible. Here, author teams have been encouraged to speculate on potential as well as proven mechanisms. In other locations such as the intestine (Rowland and Brubaker, 2008), testis (Hoffman, 2008) and skin (Paus et al., 2008), the presence of true adult stem cells is established (listed in bold type in Table 1). In this setting, authors have included the potential for endocrine and growth factor regulation that has previously been largely unscripted. A beautiful example is the regulation of haematopoiesis by parathyroid hormone (PTH) signalling (Garrett and Emerson, 2008). Historically, those interested in bone, in rheumatology or orthopaedics, have ignored the organ's role in making blood from its central marrow spaces—the preserve of haematologists. Of course, arbitrarily dividing clinical specialties is biological nonsense and with bone and blood production juxtaposed perhaps it should be expected that the major hormone orchestrating the deposition and resorption of bone by osteoblasts and osteoclasts should also turn out to regulate the haematopoietic niche. It transpires that PTH signals through the osteoblast, at least in part via the local production of insulin-like growth factor-1 (IGF1), to increase the number of haematopoietic stem cells (HSCs) resident in the marrow spaces (Calvi et al., 2003). The consequences are fascinating and provoke questions about similar cell signalling in other niches around the body. For instance, is there a similar microenvironment during gestation when PTH-related peptide (PTHrP) is more prevalent than PTH but signals through the same cell surface receptor? Similarly, during

gestation where fetal haematopoiesis predominates in the liver, is IGF2 more important than IGF1, recognizing that both hormones can act via the type 1 IGF receptor (IGF1R)?

Several articles here and elsewhere report IGF signalling as a 'funnel' for diverse inter-cellular communication. Ex vivo, IGF2 has recently been proposed as a major mediator of human embryonic stem cell (ESC) renewal (Bendall et al., 2007); fibroblast growth factor (FGF)-2 stimulating its production by differentiated cells on the periphery of ESC colonies. In this issue, Rowland and Brubaker discuss the role of glucagon-like peptide 2 (GLP-2) signalling in regulating intestinal stem cells and the renewal of the gut epithelium (Rowland and Brubaker, 2008). As with PTH in bone, GLP-2 in gut is proposed to act via IGF1. GLP-1 and GLP-2 are both derived from intestinal L-cells by the action of prohormone convertase 1/3 on proglucagon (Drucker, 2005). Whereas GLP-1 is an incretin, enhancing insulin secretion (Drucker, 2006), GLP-2 is intestinotrophic; increasing mucosal thickness and surface area, and favouring crypt cell proliferation over apoptosis in both the small and large intestine (Brubaker and Drucker, 2004; Drucker et al., 1996). Whether these effects are targeted directly at the intestinal stem cell or include actions on the transit amplifying cells can be anticipated from the next phase of cell-specific gene targeting experiments in mice. In this issue, Ishizuya-Oka and Shi complement the article by Rowland and Brubaker by reviewing the amazing role of thyroid hormone in remodelling the amphibian gut as part of amphibian metamorphosis (Ishizuya-Oka and Shi, 2008). It seemed timely to consider whether insight from this fascinating phase of *Xenopus* development might be beneficial for understanding day-to-day mammalian intestinal renewal. The topic is challenging as the genome-wide tools of microarray and genomic 'ChIP-on-ChIP' arrays, readily available and comprehensive for major mammalian model species, are only just becoming accessible for study of *Xenopus*. It transpires that the gut remodelling in *Xenopus* is most likely via the genomic actions of T3 (Buchholz et al., 2004; Ishizuya-Oka and Shi, 2008). In mice, inactivation of thyroid hormone receptor (TR) α causes underdeveloped intestinal crypts and villi (Plateroti et al.,

1999; Plateroti et al., 2001). Although conjectural, perhaps the common contribution of thyroid hormone signalling across these species is twofold: establishing the appropriate niche for adult intestinal stem cells and then regulating the balance between intestinal epithelial cell proliferation, differentiation and apoptosis. In *Xenopus*, thyroid hormone signalling induces expression of epithelial cell sonic hedgehog (SHH), which promotes bone morphogenetic protein (BMP)-4 release from the sub-epithelial fibroblasts lining the niche (Ishizuya-Oka and Shi, 2008). In mice, BMP signalling is proposed to act as a brake on Wnt-mediated stem cell proliferation (Rowland and Brubaker, 2008). Correspondingly, inactivation of BMP signalling leads to polyposis, a dysregulated villus growth that can progress to malignancy. In this sense, BMP signalling is counteracting the indirect effect of GLP-2 on intestinal crypt proliferation. The discovery in *Xenopus* that TR induces expression of various matrix metalloproteinases (MMPs) suggests an additional role in establishing and modulating the local intestinal niche, a role which has parallels elsewhere. In the gut, it allows invagination of the epithelial layer into crypts during metamorphosis; in the bone marrow, MMP action converts membrane-associated kit ligand into its soluble form leading to mobilization of HSCs away from the bone marrow niche into the peripheral circulation (Garrett and Emerson, 2008).

Tiede, Arck and Paus review the hair follicle stem cell, a critical component of the skin's ability to regenerate (Paus et al., 2008). It transpires that this niche potentially harbours a local version of the hypothalamic-anterior pituitary-adrenal cortex axis but whether glucocorticoid directly targets the stem cell, or whether effects are indirect, remains unclear. The concept is similar to maintenance of the adrenal cortex, where local glucocorticoids are proposed to feedback onto and preserve the undifferentiated state of the subcapsular stem cells (Kim and Hammer, 2007). The key mediator of this state is considered to be the transcription factor, DAX1, mutation of which results in adrenal hypoplasia (Kim and Hammer, 2007) and which is also linked to ESC pluripotency (Kim et al., 2008).

Structurally, the hair follicle stem cell with its crypt-like configuration is reminiscent of the intestinal epithelium. A similar arrangement is apparent in the uterus and reviewed by Gargett and colleagues (Gargett et al., 2008). During reproductive life, if ovulation goes unfertilized the luminal epithelium regenerates on a monthly basis from basal crypt-like glands, highly congruent with an underlying stem cell population. As in the skin and intestine, epithelial cells at the base of crypts communicate with underlying stromal cells and are intimately associated with the vasculature. As in other sites, IGF1 is a proliferative influence, however, the process is interesting for its modulation by IGF binding proteins (IGFBPs) produced by the decidualizing (i.e. differentiating) cells; in effect, a form of negative feedback similar to that proposed earlier for glucocorticoids on adrenocortical stem cells (Kim and Hammer, 2007). In the uterus, the induction of IGFBPs by IGF signalling limits further IGF1 action. IGFBPs have been noted in the hair follicle and seem likely to be relevant (Paus et al., 2008), questioning whether this autoregulation is also true of the gut epithelium (Rowland and Brubaker, 2008) and haematopoietic niches (Garrett and Emerson, 2008). On the basis of colony formation in culture and distinct gene expression profiles, the stem or progenitor cells for the uterine epithelium are thought to be different from those for its underlying stroma (Gargett et al., 2008). Neither cell responds directly to estrogen, but the hormone, delivered by the adjacent vasculature, has indirect proliferative effects via the surrounding estrogen receptor (ER) α-positive cells of the niche. Green fluorescent protein (GFP) lineage tracing of cells expressing CD45 suggests that bone marrow-derived cells, with a phenotype akin to mesenchymal stem cells (MSCs), may contribute to the uterine regenerative process (Bratincsak et al., 2007). As such, once taken into in vitro culture, isolated uterine MSCs have given rise to progeny that resemble bone, cartilage and fat cells. This type of in vitro experiment and its application to tissue engineering is covered by Oreffo and colleagues who also reinforce the importance of the vascular microenvironment (Tare et al., 2008). During development, tissue development and differentiation must be matched by adequate vascularization for the delivery of

circulating hormones and nutrients, and the removal of metabolic waste products. Blood vessels also afford intercellular contact and signalling with endothelial cells. Thus, vasculature is critical for effective tissue repair and must impact heavily on how we devise strategies and choose scaffolds for tissue engineering in the laboratory.

Trying to recreate the in vivo niche in vitro has been challenging, arguably the reason why it has proven difficult to reliably differentiate human ESCs en masse to differentiated cell-types other than perhaps neuroprogenitors and cardiomyocytes and why transplantation therapies have yet to come to fruition. Recognizing this difficulty reinforces the application of ESCs to the potentially shorter-term goals of drug toxicity screening programmes (Cezar, 2007; Menendez et al., 2006; Suter, 2006), where cellular differentiation must be predictive but demands on absolute physiological normality are lessened. Two author teams have taken on reviewing ESC differentiation to therapeutic targets and both lean heavily on descriptions of normal in vivo development. Best et al examines beta cell differentiation from ESCs, for which very encouraging recent progress has been made but where physiological normality remains debatable (Best et al., 2008). They end by cross-referencing an article on potential resources within the adult pancreas for in vivo beta cell regeneration (Hanley et al., 2008), a field with equally exciting recent developments (Xu et al., 2008). The rationale is that even if ESC-derived therapy is unfruitful the lessons learned might still facilitate the knowledge base for a drug discovery programme that underpins in vivo beta cell regeneration (Tutter et al., 2006). A more contentious differentiation target for ESC-derived therapy is gametes for fertility treatment. In addressing this, Moore and colleagues review the literature on the differentiation of the mammalian germ cell lineage during development and relate this to their own experiences and those of others in trying to generate gametes from ESCs in the laboratory (Moore et al., 2008). One of the most striking findings has been the appearance of markers of both male and female germ cells regardless of the chromosomal sex of the starting ESCs. This argues strongly that it is not simply a genetic process but

that the developmental niche for primordial germ cells once the cells have arrived at the gonadal ridge is critical. At this point, female cells then enter meiotic arrest. Meiosis is only resumed at the time of ovulation years later. The corresponding male cells enter mitotic arrest prior to differentiation into spermatogonial stem cells (SSCs) (Hoffman, 2008). Whereas the female cells have lost all proliferative potential, these latter male cells represent a true adult stem cell population. Impressively, mouse SSCs have now been maintained in vitro and have been demonstrated to repopulate the testes of infertile mice and resume successful spermatogenesis (Hoffman, 2008). More surprisingly, SSCs taken in vitro also have the potential to give rise to multipotent germline stem cells, similar in self-renewal and differentiation capacity to ESCs (Kanatsu-Shinohara et al., 2004). In their in vivo niche, following the hormonal awakening of the hypothalamic-anterior pituitary axis at puberty, SSCs underlie continual spermatogenesis for the remainder of adult life. Marie-Claude Hofmann focuses on the role of glial cell line derived neurotrophic factor (GDNF) in regulating this process (Hoffman, 2008). GDNF is produced, mainly under the influence of FGF2, by the Sertoli cell, the cell-type that has intimate relations with the SSC. When over-expressed in mice, GDNF leads to seminoma-like germ cell tumours (GCTs), leading us to consider not just the stem cell or progenitor niche in healthy tissues, but its role in disease.

GCTs are intricately linked to stem cell biology as a number of different types retain a clear stem cell compartment amongst differentiated progeny. The fact that GCTs are more prevalent in dysplastic gonads implies that the niche is important in causing or supporting GCTs, possibly associated to GDNF signalling. One hypothesis, expounded by Rajpert-De Meyts and colleagues, is that the forerunner of many GCTs, carcinoma *in situ* (CIS) is initiated during fetal development and also contains a stem cell population (Kristensen et al., 2008). Then, mirrored by the presence or absence of the transcription factor SOX2, a feature possibly related to the developmental stage of the germ cell at tumour initiation, either a nullipotent seminoma (SOX2-negative) or a pluripotent embryonal carcinoma (EC, SOX2-

positive) arises from the CIS. The proposed initiation of CIS during fetal development, particularly in undervirilised testes, has led to speculation that endocrine disruptors are causal, backed up by data in experimental animal models (Kristensen et al., 2008). This concept, that microenvironment is influential in tumour initiation, maintenance or progression, is not limited to GCTs. As carincoma of the liver is more prevalent on the background of cirrhosis, so Berry and colleagues describe the increased stromal compartment that accompanies prostate cancer (Berry et al., 2008). Rather like the gut remodelling discussed earlier, this stromal niche for the epithelial tumour cells is notable for the expression of MMPs. Presumably, the concept of niche for cancer stem cells also extends to metastasis where cells might 'seed' ectopic locations with sufficiently acceptable matrix and into which vascularisation follows. Such an occurrence is not necessarily restricted to tumour (stem) cells. A similar theory could explain endometriosis, where epithelial stem or progenitor cells escape the normal uterine environment and set up monthly regenerative cycles in ectopic locations, such as the peritoneum of the abdominal cavity (Gargett et al., 2008).

In the CNS, regulated electrical activity is an intriguing additional component of a healthy stem or progenitor cell niche. In this issue, Gray discusses the abnormal activation of neurogenesis in the hippocampus caused by epileptic seizures (Gray, 2008). The data are persuasive that the response is mediated, at least in part, by Neuropeptide Y (NPY) along with FGF2 and serotonin, and raise the potential that modulation of CNS stem or progenitor cell activity carries therapeutic implications for mood control, cognitive function and memory.

Since the discovery of embryonic stem cells, the media portrayal of the stem cell field has arguably overplayed the futuristic concept of stem cell transplantation as a kind of 'spare parts' solution to longevity (Kitzinger and Williams, 2005). Differentiating human ESCs to therapeutic end-points is still an important goal for transplantation therapy and there has been tangible progress. However, their application in toxicology and drug discovery programmes is also important and arguably more likely to

deliver benefit in the shorter term (Suter, 2006; Tutter et al., 2006). Furthermore, the realization that similar hormones and growth factors signal in discrete stem or progenitor cell niches around the body with diverse consequences both in health and disease opens up new avenues for modulatory drugs aimed at managing chronic disorders and targeted cancer treatments as well as organ and tissue regeneration (Table 2).

Acknowledgements

The author is very grateful to all contributing authors for their efforts, to referees for their time in assisting peer review and to Ilpo Huhtaniemi for valuable comments on this article. Research in the author's laboratory is funded by the MRC, EPSRC, BBSRC, Juvenile Diabetes Research Foundation, Wellcome Trust and the Kerkut Trust.

References

Bendall, S.C., Stewart, M.H., Menendez, P., George, D., Vijayaragavan, K., Werbowetski-Ogilvie, T., Ramos-Mejia, V., Rouleau, A., Yang, J., Bosse, M., Lajoie, G. and Bhatia, M., 2007. IGF and FGF cooperatively establish the regulatory stem cell niche of pluripotent human cells in vitro. Nature. 448, 1015-1021.

Berry, P.A., Maitland, N.J. and Collins, A.T., 2008. Androgen receptor signalling in prostate: effects of stromal factors on normal and cancer stem cells. Mol Cell Endocrinol.

Best, M.B., Carroll, M., Hanley, N.A. and Piper Hanley, K., 2008. Embryonic stem cells to beta-cells by understanding pancreas development. Mol Cell Endocrinol.

Bratincsak, A., Brownstein, M.J., Cassiani-Ingoni, R., Pastorino, S., Szalayova, I., Toth, Z.E., Key, S., Nemeth, K., Pickel, J. and Mezey, E., 2007. CD45-positive blood cells give rise to uterine epithelial cells in mice. Stem Cells. 25, 2820-2826.

Brubaker, P.L. and Drucker, D.J., 2004. Minireview: Glucagon-like peptides regulate cell proliferation and apoptosis in the pancreas, gut, and central nervous system. Endocrinology. 145, 2653-2659.

Buchholz, D.R., Tomita, A., Fu, L., Paul, B.D. and Shi, Y.B., 2004. Transgenic analysis reveals that thyroid hormone receptor is sufficient to mediate the thyroid hormone signal in frog metamorphosis. Mol Cell Biol. 24, 9026-9037.

Calvi, L.M., Adams, G.B., Weibrecht, K.W., Weber, J.M., Olson, D.P., Knight, M.C., Martin, R.P., Schipani, E., Divieti, P., Bringhurst, F.R., Milner, L.A., Kronenberg, H.M. and Scadden, D.T., 2003. Osteoblastic cells regulate the haematopoietic stem cell niche. Nature. 425, 841-846.

Cezar, G.G., 2007. Can human embryonic stem cells contribute to the discovery of safer and more effective drugs? Curr Opin Chem Biol. 11, 405-409.

Drucker, D.J., 2005. Biologic actions and therapeutic potential of the proglucagon-derived peptides. Nat Clin Pract Endocrinol Metab. 1, 22-31.

Drucker, D.J., 2006. The biology of incretin hormones. Cell Metab. 3, 153-165.

Drucker, D.J., Erlich, P., Asa, S.L. and Brubaker, P.L., 1996. Induction of intestinal epithelial proliferation by glucagon-like peptide 2. Proc Natl Acad Sci U S A. 93, 7911-7916.

Gargett, C.E., Chan, R.W.S. and Schwab, K.E., 2008. Hormone and growth factor signaling in endometrial renewal: role of stem/progenitor cells. Mol Cell Endocrinol.

Garrett, R.W. and Emerson, S.G., 2008. The Role of Parathyroid Hormone and Insulin-Like Growth Factors in

Hematopoietic Niches: Physiology and Pharmacology. Mol Cell Endocrinol.

Gray, W.P., 2008. Neuropeptide Y signalling on Hippocampal Stem Cells in Health and Disease. Mol Cell Endocrinol.

Hanley, N.A., Piper Hanley, K., Miettinen, P.J. and Otonkoski, T., 2008. Weighing up beta-cell mass in mice and humans: self-renewal, progenitors or stem cells? Mol Cell Endocrinol.

Hoffman, M.-C., 2008. Signaling pathways within the spermatogonial stem cell niche. Mol Cell Endocrinol.

Ishizuya-Oka, A. and Shi, Y.-B., 2008. Thyroid hormone regulation of stem cell development during intestinal remodeling. Mol Cell Endocrinol.

Kanatsu-Shinohara, M., Inoue, K., Lee, J., Yoshimoto, M., Ogonuki, N., Miki, H., Baba, S., Kato, T., Kazuki, Y., Toyokuni, S., Toyoshima, M., Niwa, O., Oshimura, M., Heike, T., Nakahata, T., Ishino, F., Ogura, A. and Shinohara, T., 2004. Generation of pluripotent stem cells from neonatal mouse testis. Cell. 119, 1001-1012.

Kim, A.C. and Hammer, G.D., 2007. Adrenocortical cells with stem/progenitor cell properties: recent advances. Mol Cell Endocrinol. 265-266, 10-16.

Kim, J., Chu, J., Shen, X., Wang, J. and Orkin, S.H., 2008. An extended transcriptional network for pluripotency of embryonic stem cells. Cell. 132, 1049-1061.

Kitzinger, J. and Williams, C., 2005. Forecasting science futures: legitimising hope and calming fears in the embryo stem cell debate. Soc Sci Med. 61, 731-740.

Kristensen, D.M., Sonne, S.B., Ottesen, A.M., Perrett, R.M., Nielsen, J.E., Almstrup, K., Skakkebaek, N.E., Leffers, H. and Rajpert-De Meyts, E., 2008. Origin of pluripotent germ cell tumours: The role of microenvironment during embryonic development. Mol Cell Endocrinol.

Menendez, P., Bueno, C. and Wang, L., 2006. Human embryonic stem cells: A journey beyond cell replacement therapies. Cytotherapy. 8, 530-541.

Moore, H.D., Udayashankar, R. and Aflatoonian, B., 2008. Stem cells for reproductive medicine. Mol Cell Endocrinol.

Paus, R., Arck, P. and Tiede, S., 2008. (Neuro-) endocrinology of epithelial hair follicle stem cells. Mol Cell Endocrinol.

Plateroti, M., Chassande, O., Fraichard, A., Gauthier, K., Freund, J.N., Samarut, J. and Kedinger, M., 1999. Involvement of T3Ralpha- and beta-receptor subtypes in mediation of T3 functions during postnatal murine intestinal development. Gastroenterology. 116, 1367-1378.

Plateroti, M., Gauthier, K., Domon-Dell, C., Freund, J.N., Samarut, J. and Chassande, O., 2001. Functional interference between thyroid hormone receptor alpha (TRalpha) and natural truncated TRDeltaalpha isoforms in the control of intestine development. Mol Cell Biol. 21, 4761-4772.

Rowland, K.J. and Brubaker, P.L., 2008. Life in the crypt: a role for glucagon-like peptide-2? Mol Cell Endocrinol.

Suter, W., 2006. Predictive value of in vitro safety studies. Curr Opin Chem Biol. 10, 362-366.

Tare, R.S., Babister, J.C., Kanczler, J. and Oreffo, R.O.C., 2008. Skeletal Stem Cells: phenotype, biology and environmental niches informing tissue regeneration. Mol Cell Endocrinol.

Tutter, A.V., Baltus, G.A. and Kadam, S., 2006. Embryonic stem cells: a great hope for a new era of medicine. Curr Opin Drug Discov Devel. 9, 169-175.

Xu, X., D'Hoker, J., Stange, G., Bonne, S., De Leu, N., Xiao, X., Van de Casteele, M., Mellitzer, G., Ling, Z., Pipeleers, D., Bouwens, L., Scharfmann, R., Gradwohl, G. and Heimberg, H., 2008. Beta cells can be generated from endogenous progenitors in injured adult mouse pancreas. Cell. 132, 197-207.

Definitions			
Stem cell	Long-term self-renewal combined with the ability to give rise to differentiated cell-types		
Progenitor cell	Limited or no capacity for self-renewal but an ability to give rise to differentiated cell-types		
Location	*Stem cell*	*Supportive evidence*	*Reference for this issue**
Bone marrow	**Haematopoietic stem cell** Mesenchymal stem cell	**Regular renewal of blood cells and the success of bone marrow transplantation** Ability to form cartilage, bone, muscle and fat but precise characterization of the underlying stem cell phenotype remains debated	(Garrett and Emerson, 2008) (Tare et al., 2008)
Intestine	**Intestinal epithelial stem cell**	**Regular renewal of gut epithelium**	(Rowland and Brubaker, 2008)
Skin / Hair follicle	**Epithelial stem cell**	**Regular renewal of skin and the success of skin grafting**	(Paus et al., 2008)
Testis	**Spermatogonial stem cell** Carcinoma in situ stem cell	**Regular production of sperm and transplantable stem cell populations** Emerging concept that stem cells underlie germ cell tumours	(Hoffman, 2008) (Kristensen et al., 2008)
Adrenal gland	Adrenocortical stem cell	Ability to repopulate the different adrenocortical cell-types from very few precursor-like or possibly true subcapsular stem cells	(Kim and Hammer, 2007)*
Brain	Hippocampal stem cell	Emerging evidence that the CNS is not comprised of entirely post-mitotic cells and that stem cell activity may underlie critical aspects of brain function	(Gray, 2008)
Uterus	Epithelial & stromal stem cells	Monthly menstrual cycle with endometrial renewal	(Gargett et al., 2008)
Prostate	Prostate stem cell / Prostate cancer stem cell	The emerging concept that stem cells underlie prostate cancer	(Berry et al., 2008)
Pancreas	Adult beta cell stem cell	Highly contentious but evidence that ductal or periductal cell populations retain an ability to re-initiate beta cell differentiation	(Hanley et al., 2008)

Table 1. Definitions and a summary of the organ regeneration covered in this issue.

Bold type is used for proven adult stem cell populations. References to associated articles in this issue are listed plus one (*) from a preceding issue of *Mol Cell Endocrinol.*

Hormone	*Stem or progenitor cell population*	*Potential novel clinical application?*	*Reference to this issue*
PTH	Haematopoietic stem cell	Promotion of haematopoiesis	(Garrett and Emerson, 2008)
NPY	Neural stem cell / neuroprogenitor	Mood control, cognition and memory	(Gray, 2008)
Various	Hair follicle stem cells	Alopecia or treating hirsuitism	(Paus et al., 2008)
GLP-2	Intestinal stem cell	Protective cover or accelerated recovery of gut epithelial lining during or following chemotherapy	(Rowland and Brubaker, 2008)

Table 2. Potential futuristic exploitation from modulating hormone or growth factor signalling on endogenous stem cell populations.