

Adult Gland Derived Stem Cells (Gdscs); Potentials, Hurdles and Expectations

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Abstract

In the past decades, a progressively escalating international pool of information regarding stem cells research and their applications was periodically accumulating. Among the famous, well-established stem cells sources and lines, a new source appeared that was derived from the adult glands.

Despite the long time theories speculating that the adult glands, as most of adult tissues, harbor their own stem cell pools, only recently those cells were isolated, characterized and successfully propagated from the glands.

Although some of them are still in the immature phase of research, but within a few years, the newly identified glands derived stem cell lines proved their potency in multiple fields, with the relative ease of their harvesting and propagation compared to other sources.

For the first time in literature, a definitive focus is given in this review to the adult gland derived stem cells, in a trial to understand and track their potentials as a new innovative form of stem cells for future applications.

Keywords: Glands; Stem cells; Regenerative medicine

Introduction

Adult (non-embryonic, postnatal somatic) stem cell is an undifferentiated cell found among differentiated cells in a tissue or organ that has the ability to renew itself (Multipotency) [1].

Growing attention has focused on organ specific adult stem cells, both to better understand how injured organs regenerate and as a therapeutic target for disease modulation [2,3]. It was originally thought that the adult mammalian stem cells were only present in organs such as blood, skin, gut, testes and the respiratory tract, which have high cell turnover rates. It was proven, however, that most if not all, adult organs contain stem cells, or at least can produce stem cells in culture [4,5].

Adult stem cells derived from the bone marrow have been used for more than 40 years for treatment of hematological disorders. Since the identification of the first adult mouse bone marrow stem cells, it was shown that transplantations of the Haemopoietic stem cells (HSCs) isolated from the bone marrow, could reconstitute the depleted bone marrow following irradiation [6].

Following this discovery, Friedenstein in 1974 noticed another cell type in the bone marrow explants, initially called the fibroblast colony-forming cells, now referred to as Marrow-derived or Mesenchymal Stem Cells (MSCs) [7]. In contrast to HSCs, MSCs can be grown more easily and can differentiate into mesoderm-derived tissues, while HSCs can re-constitute the haemopoietic system. MSCs can be selectively grown into bone cells (osteocytes) [8], fat cells (adipocytes) [9] and cartilage cells (chondrocytes) [10] which made them an attractive choice for bone and cartilage tissue engineering as autologous transplants [11,12]. Moreover, they are now considered a routine medical procedure in treating leukemia patients in addition to HSCs [13].

The discovery of adult stem cells in the CNS was first inferred from the evidence of neuronal turnover in the olfactory bulb and hippocampus [14,15]. This discovery of what was called afterwards Neuronal Stem cells (NSCs) in an organ that was previously thought to be largely immutable following embryogenesis, opened new avenues of

investigation in regenerative medicine concerning the role of such stem cells in Parkinsonism and Alzheimer's diseases [16,17].

In this review, we highlight some of the particularly promising sources of potent adult stem cells; the glandular tissues derived ones, elucidating their importance and future potentials in diseases management.

Pancreas Derived Stem Cells (PSCs)

Pancreas is a unique organ with a closely integrated admixture of exocrine and endocrine tissues. In the view of the success of pancreatic islet transplantation trials, especially after development of the Edmonton Protocol in 1990 and its publish in 2000 [18,19], beta-cell stem or progenitor cells were seen as a potential source for the preparation of a transplantable insulin-producing tissue [20].

Thus, several adult islet/beta-cell progenitors derived from pancreas, liver, and bone marrow, were studied [21]. Moreover, it was proven that the pancreas have Pancreas-derived Multipotent Precursor cells PMPs as described by Seaberg, that express both neural and pancreatic precursor markers [22]. Possible progenitors have been hypothesized to reside within the pancreatic ductal epithelium [23], acinar tissue and/or pancreatic small cells [24].

Although the transplantation of islet grafts containing higher numbers of ductal epithelial cells results in a better clinical outcome [25], several in vitro attempts to isolate beta-cell progenitors thought

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Received June 15, 2014; **Accepted** August 27, 2014; **Published** August 29, 2014

Citation: Salem H, Ismail M, Seify H (2014) Adult Gland Derived Stem Cells (Gdscs); Potentials, Hurdles and Expectations. J Stem Cell Res Ther 4: 228. doi:10.4172/2157-7633.1000228

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to reside within the human ductal and acinar epithelium have been inconsistent till today [26-29].

Earlier, Choi followed by Seeberger proved that stem cells isolated from different parts of the adult pancreas are able to cross-lineage boundaries in vitro, in addition to its differentiation into endodermal and mesodermal cells [30,31]. Also, the exocrine acinary part of the pancreas, particularly periacinary or dedifferentiated acinary cells, was considered to be another source of stem cells [32].

Surprisingly afterwards, Kruse et al. proved that cells isolated from the exocrine parts of the adult pancreas have a remarkable ability for self-renewal together with a great plasticity potential. These cells were able to differentiate into various cell types representing all three germ layers. Those cells demonstrated (i) typical stem/progenitor cell markers (Alk. Phos., SSEA-1, Oct-4, CD9, Nestin, Pax6, CD44, alpha-fetoprotein), (ii) have the potential to differentiate into lineages of all three germ layers in vitro, (iii) clonal analysis revealed that even cell lines derived from a single cell have stem/progenitor cell properties, (iv) external stimuli can activate the generation of certain cell types (e.g. alpha-smooth muscle actin upon retinoic acid stimulation). Those cells were called Pancreatic Stellate Cells based on their morphological appearance or more commonly Pancreatic Stem Cells (PSCs) [33,34].

In a study that compared two stem cell populations (Skin versus Pancreatic stem cells) concerning their phenotypic characterization, stem cells characteristics and differentiation across lineage boundaries, it was surprisingly proved that the Skin-derived human adult stem cells share many features with the Pancreatic-derived human stem cells, this opened the gate for a new way of tackling those PSCs concerning their medical applications and their potential role in skin regeneration and wound healing [35]. In this view, those cells were then successfully tested for their potentials in wound healing [36], and for their ability to enhance the wound vicinity vascularity [37]. Also they were used for defective myocardial tissue repair proving a superior intra-myocardial homing of PSCs in comparison to MSCs therapy [38].

Salivary Glands Stem cells

Salivary glands are derived from the endoderm and the ectoderm that participate in organogenesis [39]. They consist of many cell types, including duct epithelium, acinar, mesenchymal, and neuronal cells [40]. Acinar cells secrete amylase into the digestive tract. This feature resembles the pancreatic exocrine system. Moreover, Salivary glands have been described as a source of stem cells in mice and rats following tissue damage [41,42] and there have been experimental evidences that stem cells can be isolated from intact, non-damaged rat submandibular glands [43]. The existence of salivary gland stem cells has been postulated, although it remained unclear in which compartment of the gland they reside. Some authors suggested the intercalated ducts, whereas others favored the theory that MSCs are generally present in a perivascular niche [44].

In 2008, Rotter et al. [45] published the first paper to describe the isolation and characterization of adult human stem cells from normal parotid gland, these cells followed an amplification period of three to five passages.

As a trial to salvage the function of the Salivary gland specially in patients with head and neck irradiation, Bone marrow-derived stem cells (BMCs) were previously suggested as an easy accessible source for multipotent stem cells that could potentially transdifferentiate and/or repair other non-hematopoietic organs [46-49], including salivary glands [50].

However, the use of BMCs in solid tissue repair is surrounded by controversies and limited effects. Transplantation of salivary gland stem cells was then proven to be a more adequate and an elegant way for therapy after successful isolation of stem cells from both human Parotid and submandibular glands [51].

Salivary gland cancers are relatively rare but constitute a highly significant public health issue due to the lack of effective treatments. In particular, patients with mucoepidermoid carcinoma or adenoid cystic carcinoma, the two most common salivary malignancies, have low long-term survival rates due to the lack of response to current therapies. Considering the role of Cancer Stem Cells (CSCs) in resistance to therapy with other tumor types, it is possible that this unique sub-population of salivary gland stem cells is involved in the resistance of salivary gland tumors to treatment [52]. A deeper understanding of the underlying cellular biomechanics of the salivary glands and the potential of their stem cells may be a good option to treat post-tumors radiation-induced Xerostomia [53].

Due to their large number and superficial distribution in the labial mucosa, Minor salivary glands were recently proposed as an easily accessible source of adult stem/progenitor cells for regenerative therapies of glandular organs with parenchymal pathology [54]. In a novel study, pulse chase strategy allowed the identification of slow cycling, label retaining cells (LRC) of minor salivary glands that preferentially localize in the basal layer of the lower excretory duct, with few in the acini possessing stem cells characteristics. Engraftment of isolated salivary glands LRC in vivo demonstrated their ability to differentiate into CK5 (basal layer marker) and CK8 (luminal layer marker) positive structures [55].

Still, in the salivary glands research field, a single stem cell has not been identified that gives rise to all epithelial cell types within the gland. It is also not known whether a number of different lineage-biased stem cell populations or subtypes exist and how these differ from progenitor cells [56,57].

Sweat Glands Stem cells

Skin is a readily accessible tissue for the isolation of adult autologous stem cells in contrast to most of the other tissues. The human body is covered with several million sweat glands. Two major types of sweat glands exist in the Human skin; eccrine and apocrine. The eccrine glands, which are widely distributed over the human body, have ducts that open directly onto the skin surface enabling them to secrete water and salts. In contrast, the apocrine sweat glands, which are present in hairy areas, are appendages of the hair follicle and release their fluid through the follicle's orifice. In addition, apocrine sweat glands shed off their necrotic cell parts in the form of an oily substance [58,59].

Extensive Lineage tracing with transgenic mice lines has been used to track epithelial progenitors and their progeny [60,61]. Recently, the existence of multipotent and unipotent progenitors in the sweat glands was proven using transgenic mice [62], and through tracing the Nestin-positive multipotent stem cells directly isolated from human sweat glands specimens [63].

Former studies using lineage tracing and mouse models proved the role played by both the epidermis and the hair follicles stem cells contributing in the wound repair [64-68].

Due to the abundance of sweat glands in relation to hair follicles in the majority of human skin areas, it has been hypothesized that another source of progenitors and/or stem cells within the sweat apparatus (duct and gland) can contribute to the skin wound repair [69-71].

Interestingly, new mouse models permitted definitive assessment of the source of stem cells in wound healing process. Marked cells from the eccrine sweat ducts migrated upward to repair the epidermis within 3 days after a superficial scratch wound. Intraepidermal sweat ducts were reconstructed within 2 weeks. Notably, these reconstructed ducts were derived from cells of the sweat apparatus and not the epidermis. Moreover, only basal progenitors within the sweat ducts, and not the secretory portion of the glands, responded and proliferated to repairing the duct orifice after injury with restoration of sweating [62]. These results provided compelling evidence supporting the notion that the sweat duct is the growth center which repairs the ductal orifice extending through the epidermis to the skin surface [72].

Another study readdressed this issue using the human skin. By immunohistochemistry and computer-assisted three-dimensional reconstruction, researchers concluded that eccrine sweat glands contribute significantly to the reepithelialization after partial-thickness wounds. This opened the gate for enormous wide range potential clinical applications, namely in cases of extensive burns and massive skin loss [73].

In the last decade, *in vivo* transplantation had been used to assess the regenerative potential at a single-cell level for various ectodermal appendages as a trial for an innovative management of burns. Intriguingly, despite their unipotent behavior in the adult gland, when myoepithelial cells are purified from adult sweat glands, they recreate the adult sweat glands. These findings suggest that the myoepithelial cells retain multipotent (bipotent) potential that can be unleashed when challenged to *de novo* morphogenesis [72].

Mammary Gland Stem Cells (MaSCs)

Over 50 years ago, researchers postulated the existence of multipotent mammary stem cells due to the fact that mammary epithelium is able to undergo multiple rounds of proliferation, differentiation and apoptosis with pregnancy. Experiments revealed that neither the developmental state nor the reproductive history of the gland had a significant impact on the longevity of the mammary transplants [74,75].

The study of mammary stem cells biology in the mouse actually began with the pioneering studies of Deome et al. when a serial transplantation of mammary tissues into the cleared mammary fat pad of syngenic mice was done [76-78]. They demonstrated that the adult mammary gland contained cells that were capable of reconstituting a complete and functional mammary gland with normal ductal tree and hormonal response in the epithelium-divested fat pad of the transplant recipient [79].

Subsequent studies supported the old notion of the cells residing throughout the entire intact epithelial tree, that are capable of regenerating an entire mammary gland, and that they persist through various developmental states [80].

A strategy was used to isolate MaSCs relied upon a feature believed to be a key mechanism of DNA replication during stem cells division. During their division, certain adult stem cells preferentially retain one of their DNA strands throughout multiple divisions in order to protect against the formation of deleterious mutations that occur with replication [81,82]. By performing pulse chase experiments with DNA labels, Smith et al. showed that there was a population of cells within the mammary gland, which retained their DNA label through asymmetric segregation of DNA strands. These cells were still actively dividing and featured stem cell characteristics [83].

However, It was not until 2006 that self-renewing multipotent stem cells were successfully isolated from the mammary gland by fluorescent activated cell sorting (FACS), detecting the cell surface markers CD24 (heat stable integrin) and CD29 (β 1-integrin) in mouse mammary tissue [84,85]. CD49f (α 6-integrin) and EpCAM positive cells were then isolated from the human mammary tissues [86,87]. The CD29 protein is not just a surrogate marker for MaSCs but is actually functionally important, as CD29 ablation in the basal compartment is reported to effectively reduce MaSC activity [88].

Another study showed that with the use of a GFP reporter driven by the *s*-SHIP promoter, GFP+ replicating active MaSCs can be identified in cap cells at puberty and basal alveolar bud cells in pregnancy, but not in adult virgin animals, or in mammary tissues during lactation or involution stages [89].

A major limitation of both the morphological and the label retention methods is that they do not allow easy isolation of large numbers of pure MaSC populations for use in *in vitro* or *in vivo* assays [90]. With respect to the human mammary gland, identification of authentic MaSCs is considered a greater challenge due to the difficulty in obtaining normal tissue samples and the lack of an ideal *in vitro* reconstitution system. Nevertheless, various attempts have been made to characterize human MaSCs both *in vitro* and *in vivo* [91].

As a trial to unravel this mystery, taking into consideration the analogous embryonic development of both mammary glands and sweat glands from ectodermal appendages [92], a latest study applied the already established isolation and propagation protocols used for salivary and sweat gland-derived stem cells, to the harvest of MaSCs from the mammary tissue of human donors via conventional cell culture, using a similar way to the older technique of breast milk-derived stem cells [93], demonstrating a consistent isolation, propagation and identification of CK19+ nestin-positive MaSCs and with characterization of the cell populations derived from both genders [94].

Lacrimal Gland Derived Stem Cells

A relatively new and particularly unique field of stem cells research due to the rarity of the needed *in vitro* human specimens for study.

The lacrimal gland is made up of acini, ducts, nerves, myoepithelial cells, and plasma cells secreting a tear film interface between the external environment and the ocular surface [95]. Approximately 80% of the gland are the acinar cells, which secrete electrolytes, water, and proteins [96].

Dry eye syndrome (DES) is caused by inadequate quantity or quality of tears. Although there are numerous well-known tear substitutes that can be used to temporarily lubricate the eye, there is actually no curative treatment for the dry eye syndrome [97,98]. Cell therapy involving replacement of the gland is a promising alternative for providing long-term relief to such patients [99].

After an experimentally induced inflammation, Samantha et al previously reported an increasing number of stem/progenitor cells present in the murine lacrimal gland during the repair phase. These cells were found to be nestin positive, and some of them expressed α -smooth muscle actin (α -SMA), suggesting a common source of stem cells between myoepithelial cells and acinar cells in the lacrimal gland [100,101].

Shortly afterwards, the same research group suggested that an Epithelial-Mesenchymal transition (EMT) is induced during the repair of the lacrimal gland to generate Mesenchymal stem cells (MSCs)

that migrate to the site of injury initiating repair, followed then by the activation of Mesenchymal-Epithelial Transition (MET) to form acinar and ductal epithelial cells with the contribution of several transcription factors (Snai1, Snai2, ZEB1 and ZEB2) [102-104].

While lacrimal gland cultures from animal sources are well established [105,106], similar evidence from humans is limited. Thus, a newly established study documented what could be the first successful method of isolating and culturing functionally competent fresh human lacrimal gland cells, using a cocktail of collagenase and hyaluronidase with Matrigel substrate. The established cultures were maintained in vitro for 30–35 days, providing evidence for the presence of putative stem cells in the tissues that express ABCG2 and ALDH1 stem cell markers. In addition, the cultures lead to the formation of spheres similar to the well documented Salispheres [106] and Prostatespheres [107] in their cellular organization [99,108].

The promising discovery of stem cells in the lacrimal gland is an important finding on the path to salvage a damaged gland in the future.

Major Debates and Hurdles

Neo-genesis versus self-duplication of Pancreas derived stem cells

It is worth to be mentioned that in the past several years a wealth of new data on the origin of differentiated cells in the embryonic and adult pancreas have been accumulating. Before the era of genetic lineage tracing, we were inclined to accept the histological evidence of neogenesis, particularly following injury [109]. This view became more skeptical and extremely debatable once the lineage tracing studies revealed that the pre-existing β -cell could account for both growth and regeneration [110,111]. It was shown that Ductal cells do not generate endocrine cells following streptozotocin (STZ)-induced β -cell ablation, Solar and colleagues failed to observe β -cell regeneration from ductal cells following alloxan-mediated β -cell ablation and subsequent treatment with epidermal growth factor and gastrin [112].

Moreover, compelling opposing evidence showed that pancreatic duct ligation (PDL) could induce Ngn3-dependent islet neogenesis. Ngn3 is not normally expressed in the adult pancreas, even after pancreatectomy. As a regulator of pancreatic endocrine formation, Ngn3 expression was shown to be initiated in duct cells, and persisted into new islet cells, boosting the insulin dependent β -cells formation. [113,114]. Combining techniques, Chung et al. reported a recovery of β -cell mass within two weeks after alloxan administration when combined with PDL [115]. However, the origin of β cells in this so-called “alloxan+PDL” model was not tested through the use of genetic lineage tracing studies [116].

Two major concerns remain; first, not knowing the exact triggering stimulus of the endocrine differentiation in utero or in adults following PDL makes it hard to design rational culture conditions for optimization. Second, most pancreatic cell preparations are contaminated by pre-existing β -cells. Survival and expansion of those β -cells during culture will make it hard to detect true neogenesis. This might imply that a phenomenon widely interpreted as neogenesis is actually nothing but an expansion of the pre-existing islet cells in vitro, or else that islet precursors express a marker, NCAM, generally assumed to be specific to the differentiated endocrine cells [117].

Radiotherapy and Salivary Glands

Regretfully, most of the head and neck cancer patients are of old

age and have been suggested to respond dramatically to the deleterious effects of radiation on the salivary glands [118].

Moreover, a reduction in the salisphere-forming capability of cells from salivary gland of old age is reported [119]. Combined with the unfortunate fact that prior to radiotherapy, only a small piece of tissue from the patient could be obtained makes it essential to multiply the cells before transplantation, and it is therefore of utmost importance to solve the problem of lacking protocols that safely permit this.

Current in vitro culture, self-renewal, and differentiation assays open new possibilities for the screening of novel factors and genes that may be useful tools for stem cells amplification. The involvement of Notch signaling pathway has been implicated in postnatal salivary gland development and regeneration, and the protective effects of both KGF treatment and the transiently activated Wnt pathway against radiation-induced damage of the salivary glands have been suggested [120,121].

Although consensus is that some form of the salivary gland cellular therapy is feasible to increase the quality of life of head and neck cancer patients particularly post radiotherapy, considerable hurdles facing the development of a cellular therapy based upon a prolonged in vitro culture that can affect the expression of cell surface markers, which define this hierarchy [122].

Generally, Radiotherapy treatment schedules with curative intent last between 5 and 7 weeks, not including the extra time required for biopsy of the salivary glands pre-treatment. In an ideal situation, transplantation should be performed as soon as possible after radiotherapy, before tissue fibrosis kicks in, which is likely to be detrimental to cell engraftment. Thus, cells will probably be cultured briefly during this 5–7 weeks period and then undergo cryopreservation till the desired time point. Both manipulations techniques carry their own challenges [53,123].

Mammary gland stem cells (MaSCs) and Tumor-genesis

Studies using avian retrovirus-mediated introduction of oncogenes into a small subset of somatic mammary cells suggest that polyoma middle T antigen (PyMT) preferentially transform stem/progenitor cells. These observations suggest that stem/progenitor cells in the mammary gland may be especially susceptible to oncogenic transformation. Whether more differentiated cells may also be transformed by particular oncogenes is actively debated; it is presently unclear whether stem cells or differentiated mammary cells are more susceptible to transformation by individual oncogenes [124].

A common long time debate with all forms of stem cells, but

CSC Marker	Associated Tumor Type(s)
CD133	Brain, Colon, Liver, lung, Ovarian, pancreas, prostate
CD44	Colorectal, head and neck squamous cell carcinoma, Liver, ovarian, Prostate
CD24**	Breast, Pancreas
CD90	Breast, liver, Lung
CD34	AML, Lung
CD117	Lung, Ovarian
CD20	Melanoma
ALDH	Breast, Liver

** CD24 is a common marker between normal Mammary gland stem cells (MaSCs) and Cancer stem cells (CSCs)

Table 1: Commonly used markers for CSCs as suggested by Fabian et al. with established breast tissue markers seen among them [127].

Glandular cell source	Culture type	Suggested markers +	Reference
Pancreas	Monolayer	<ul style="list-style-type: none"> Ductal cell: CAII and CK19 Endocrine cell: PDX-1 and Ngn3 and GLUT1, VDCC Expansion: SMA and Vimentin *Stemness: Oct4, ABCG2, SCF and CD133 	Zhang et al. [128]
Salivary	Salisphere Monolayer	<ul style="list-style-type: none"> CD34, CD117, ALDH, CD90, CD44 CD49f, CD29, CD24, CD133 	Pringle et al. [53]
Sweat	Monolayer	<ul style="list-style-type: none"> Gland: NKAα, ATP1a1 K19 Luminal cell: K8, K18 Myoepithelial cell: K5, K14 *Stemness: Nestin, Id6, Oct4, SOX2 	Lu et al. [62] Nagel et al. [63]
Mammary	Monolayer Mammosphere	<ul style="list-style-type: none"> Mammary cell: CD19, CALLA, ESA, MUC-1 Duct cell: CD24 Mammospheres: CD105 *Stemness: Nestin, CD9, CD29, CD44, and CD81 	Hebbard et al. [129] Liu et al. [126] Richter et al. [92] Liao et al. [130]

* Cells show different Stem cell markers (Stemness) throughout different culture passages

+ All gland derived cells showed markers of differentiation to the three germ layers

Table 2: Summary of the suggested cellular markers of different types of gland derived stem cells by some authors.

particularly crucial with MaSCs is that the normal mammary stem cells share the cancer stem cells (CSCs) several important properties, including the ability to self-renew and to undergo differentiation (Table 1). It was proven that the transcriptional programs that control luminal and basal lineage identity in the normal mammary epithelium as well as the progenitor and stem cell function, are active in breast cancers and show distinct associations with different disease subtypes. Also active in some tumors is the epithelial to mesenchymal transition (EMT) program, which endows carcinoma, cells with mesenchymal as well as stem cell traits [125].

There has been lots of controversy about the nature of the cells that serve as targets of transformation [126]. Therefore, it is of an urgent importance to properly identify, label and characterize the MaSCs and study their differentiation potentials in response to various deleterious stimuli as a trial to understand the pathogenesis of breast tumors, in order to provide innovative solutions for breast cancers, meanwhile avoiding transfusing patients with a tumor generating time bomb.

Future Perspectives

Due to expanding nature of the field and the accumulation of vast new information about them, the need is exponentially growing to focus separately on the adult gland-derived stem cells as a continuous supply of stem cells and to our knowledge; this is the first review that takes that matter into consideration.

The available different forms of adult gland derived stem cells are not fully understood regarding their mode of action, characters, fully discriminating individual type markers (Table 2) and long-term effects, which is yet to be investigated. Nevertheless, they offer possible new supply for treatment of multiple medical problems (eg: B-cell deficiency, lacrimal glands dysfunction, salivary tumors, burns and skin regeneration). Still, the techniques and methods for practical application of such innovative treatments are far from optimization, which makes it invaluable to have more focused future trials on exploring their potentials and to optimize their medical use.

Acknowledgment

The first author would like to express all due respect to fellow colleagues and mentors in Germany; Prof. Dr. H-G Machens, Prof. Dr. C Kruse, Dr. D Rapoport, Dr. P Ciba, Dr. A Richter and S Nagel. Also, all gratitude for the continuous efforts, and the generous support of friends and colleagues at the KAFM, Cairo University, Egypt.

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