

Emerging Science, Emerging Ethical Issues : Who Should Fund Innate Alloimmunity-suppressing Drugs ?

W. G. Land *, Th. Gutmann**, A. S. Daar***

* Ludwig-Maximilians-University, Munich, Germany and c/o Baskent University, Ankara, Turkey ; ** Chair for Civil Law, Philosophy of Law and Medical Law, University of Muenster, Muenster, Germany ; *** Massey College University of Toronto, Toronto, Canada.

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Abstract. An emerging body of evidence suggests that the innate immune system plays a critical role in allograft rejection. Any injury to the donor organ, e.g. the reperfusion injury, induces an inflammatory milieu in the allograft which appears to be the initial event for activation of the innate immune system. Injury – induced intragraft damage- associated molecular patterns (DAMPs) are recognized by donor-derived and recipient-derived, TLR4/2-bearing immature dendritic cells (iDCs). After recognition, these cells mature and initiate allorecognition / alloactivation in the lymphoid system of the recipient. Indeed, the key “innate” event, leading to activation of the adaptive alloimmune response, is the injury- induced, TLR4-triggered, and NF κ B-mediated maturation of DCs (“innate alloimmunity”).

Time-restricted treatment of innate immune events would include 1) treatment of the donor during organ removal, 2) in-situ / ex-vivo treatment of the donor organs alone, and 3) treatment of the recipient during allograft reperfusion and immediately postoperatively.

Treatment modalities would include 1) minimization of the oxidative allograft injury with the use of antioxidants ; 2) prevention of the TLR4-triggered maturation of DCs with the use of TLR4-antagonists ; 3) inhibition of complement activation with the use of complement inhibiting agents. According to data from clinical and experimental studies it can be assumed that successful suppression of innate alloimmune events results in either subsequent significant reduction in, or even complete avoidance of the currently applied adaptive alloimmunity-suppressing drugs. However, in view of the time-restricted period of treatment, and the fear to potentially destroy its own business with currently applied alloimmunity-suppressing drugs, the pharmaceutical industry is still, but quite legitimately, reluctant to invest in the high cost of clinical development of those drugs for transplant patients because there are no marketing interests. On the other hand, clinical development of innate alloimmunity-suppressing drugs is urgently warranted. But : Who should fund ? In this article, three options are explored which may contribute to a solution of the problem : 1) provision of incentives to companies for drug development ; 2) conduction of clinical trials in developing countries ; and 3) creation of a public-private professional partnership in analogy to the “European Rare Diseases Therapeutic Initiative” (ERDITI). We suggest and recommend the creation of such a partnership which may be called : “The European Initiative for the Suppression of Innate Alloimmunity” (“EISIA”). In analogy to ERDITI, the main goals of this organization should be : – to provide a streamlined facilitated process of collaboration between Academic Teams / Transplant Centres, Study Groups, and Pharma Companies to develop innate alloimmunity-suppressing drugs ; – to give Academic Teams / Transplant Centres facilitated access to a large variety of compounds, developed by companies for other indications, which can be evaluated pre-clinically and, if warranted, clinically ; – to guarantee the continuity all the way from research to development and commercialisation of the drug. If preclinical studies uncover the potential of a compound for suppressing innate alloimmune events, the Pharma Partner who has rights to this compound will either develop himself the drug for organ transplantation indication or allow its development by the academic team or a third party if he has no intentions of developing himself.

ABBREVIATIONS

AP-1 : activator protein-1
APCs : antigen-presenting cells
ATG : anti-thymocyte globulin
DAMPs : damage-associated molecular patterns
DCs : dendritic cells
ECM : extracellular matrix
ECs : endothelial cells

EDCTP : European-Developing Countries Clinical Trials Programme
EISIA : The European Initiative for Suppression of Innate Alloimmunity
ELPAT : Ethical, Legal and Psychological Aspects of Organ Transplantation
ERDITI : The European Rare Diseases Therapeutic Initiative
HSPs : heat shock proteins
HO-1 : heme oxygenase-1

iDC : immature dendritic cell
 IKK $\alpha/\beta/\gamma$: I κ B kinase $\alpha/\beta/\gamma$:
 Il-6 : interleukin 6
 IP-10 : interferon- γ inducible protein-10
 IRAK : interleukin-1-receptor- associated kinase
 IRF3 : interferon regulatory factor 3
 JNK : c-Jun-N-terminal protein kinase
 MAPKs : mitogen activated protein kinases
 MBL : mannan-binding lectin
 mDC : mature dendritic cell
 MHC : major histocompatibility complex
 MyD88 : myloid differentiation marker 88
 NF- κ B : nuclear factor - κ B
 NK cells : natural killer cells
 NKT cells : natural killer T cells
 NLRs : NOD-like receptors
 NOD : nucleotide-binding oligomerization domain (proteins)
 PAMPs : pathogen-associated molecular patterns
 RIG-I : retinoic acid – inducible gene-I
 RLRs : RIG-I-like receptors
 ROS : reactive oxygen species
 siRNA : small/short interfering RNA
 SOD : superoxide dismutase
 TAK1 : TGF-beta activated kinase 1
 TBK1 : TANK- -binding kinase 1
 TGF : tumor growth factor
 TIRAP : TIR-associated protein
 TLRs : Toll-like receptors
 TNF α : tumor necrosis factor
 TRAF 6 : TNF-receptor-associated factor 6
 TRAM : TRIF-related adaptor molecule
 Tregs : T regulatory cells
 TRIF : TIR-domain containing adaptor inducing INF- β

1. The Innate Immune System = a defense system against tissue injury

The re-discovery of the innate immune system appears to revolutionize not only immunology and transplantology but even whole medicine.

The innate immune system represents an evolutionarily highly conserved, rapid first line of host defense against invading pathogens or their components (= pathogen-associated molecular patterns-“PAMPs”). A whole family of cells is involved including macrophages, dendritic cells, innate lymphocytes (NK-, NKT- $\gamma\delta$ T cells), vascular cells, epithelial cells, adipocytes, and osteoclasts. Special pattern recognition receptors such as Toll-like receptors (TLRs), NOD-like receptors (NLRs), and RIG-I-like receptors (RLRs) are able to recognize PAMPs. After recognition, TLRs initiate intracellular signal transduction pathways via four adaptor proteins (MyD88, TIRAP, TRIF, and TRAM) that result in the activation of transcription factors such as NF κ B, AP-1, and IRF3. Transcriptional expression of genes results in full functionality of innate cells which include defense capabilities to mount proinflammatory responses (e.g. antiviral responses) and to promote mat-

uration of immature dendritic cells (iDCs). Matured DCs interact with naïve T-lymphocytes, initiate a T-cell response and, thus, represent the link to adaptive immunity (1). Importantly, DC maturation is not only mediated via TLRs but also through a direct cytokine-regulated cell-to-cell contact with innate lymphocytes following detection of pathogen-derived antigens (2). Besides cells, humoral factors such as complement and natural monoclonal IgM-antibodies represent classical instruments of the innate host defense against pathogens as well (3).

An emerging body of evidence suggests that innate immunity plays also a critical role in allograft rejection (4). Any injury to the donor organ, in particular the reactive oxygen species (ROS)-mediated reperfusion injury, induces an inflammatory milieu in the allograft which appears to be the initial key event for activation of the innate immune system. Injury – induced damage-associated molecular patterns (“DAMPs”) are generated which are either actively secreted by stressed but viable cells (such as heat shock proteins [HSPs]), or released from apoptotic/necrotic cells (such as high mobility group box-1 [HMGB1]), or represents fragments of degraded extracellular matrix proteins (ECM) (such as hyaluronan and heparan sulfate). These DAMPs are recognized by TLR4 and/or TLR2-bearing innate cells which again trigger innate signalling pathways (Fig. 1). Acute allograft injury (e.g. mediated via oxidative stress during donor brain death condition and postischemic allograft reperfusion in the recipient) induces “DAMPs” which may interact with and activate innate TLR-bearing dendritic cells (DCs) which mature and initiate the recipient’s adaptive alloimmune response leading to acute allograft rejection. Notably, DC maturation may also be triggered by intragraft innate lymphocytes following detection of injury-induced neo-antigens (2). Further, initiation of alloimmunity in the recipient’s lymphoid system is mediated through matured donor – derived DCs already residing in the graft as well as through matured recipient-derived DCs entering the graft during reperfusion. Indeed, the key “innate” event, leading to activation of the adaptive alloimmune response, is the injury- induced, TLR4/TLR2-triggered, adaptor molecules and transcription factors (e.g. NF κ B) - mediated maturation of DCs as a process supported by cell-to-cell contact with innate lymphocytes. This scenario is based on the paradigm of mature/immunogenic, versus immature-semi-immature/tolerogenic DCs which has dominated the recent literature regarding the role of these antigen-presenting cells in mediating immune homeostasis. In fact, iDCs are prone to induce regulatory T cells (Tregs) and hence, promote tolerance induction (5, 6). Humoral factors such as complement and natural monoclonal IgM-antibodies appear also to be involved in injury-induced intragraft innate immune events. New evidence suggests that natural IgM-anti-

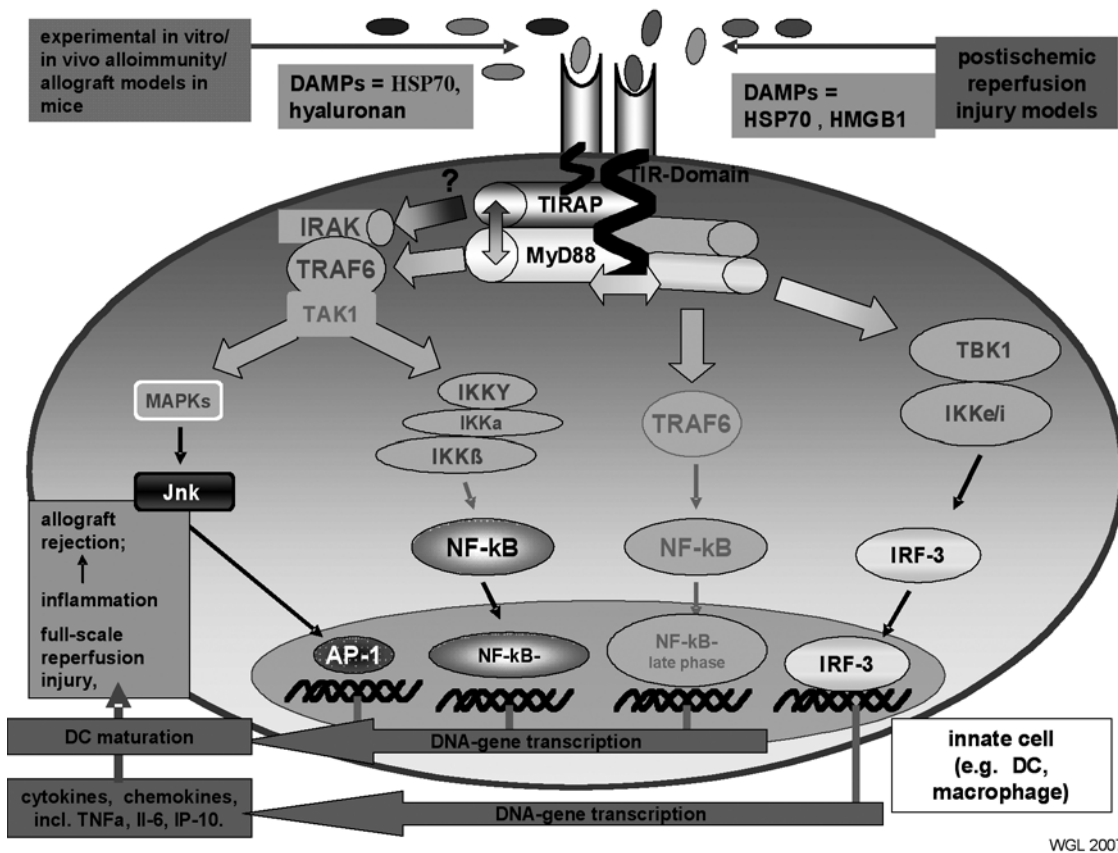


Fig. 1

Current data from experimental alloimmunity- and reperfusion injury models suggest that rejection may be mediated by the same innate signalling pathways which are critical for host defense- although, of course, not all signalling molecules have been discovered in the transplantation setting so far (dark-shadowed molecules). Nevertheless, according to current knowledge, reperfusion injury-induced DAMPs, so far discovered, interact with TLR4 and TLR2 which trigger subsequent signalling pathways. There is already evidence for a role of the adaptor molecules MyD88, TIRAP, and TRIF as well as for the transcription factors NF-κB, AP-1, and IRF3 (coloured molecules).

bodies initially bind to a reperfusion injury-induced, host-derived neo-antigen providing a binding site for mannan- binding lectin (MBL), a circulating recognition molecule which is able to activate the complement cascade (7, 8). The whole scenario may be called “innate alloimmunity” !

2. Potential treatment modalities to suppress events of the innate immune systems during organ transplantation

Per definition, treatment of innate immune events in the transplantation setting includes 1) treatment of the (brain dead/living) donor during organ removal, 2) separate in-situ / ex-vivo treatment of the donor organs alone, and 3) treatment of the recipient during allograft reperfusion (+ during the first 2-4 postoperative days). Notably, we are dealing with an a priori time-restricted therapeutic window only. Treatment modalities primarily

include (Fig. 2): 1) minimization of the allograft injury - in particular prevention of the oxidative injury in the donor and the recipient with the use of antioxidants ; 2) inhibition of the MBL-dependent activation of the complement cascade that aggravates the ROS-mediated injury ; 3) prevention of the injury-induced, TLR4-triggered, and (predominantly) NF-κB-mediated maturation of DCs, e.g. with the use of small molecule TLR4-antagonists or application of the siRNA interference technology ; 4) prevention of innate lymphocyte-triggered DC maturation by deletion of intragraft innate lymphocytes with the use of polyclonal/monoclonal anti-T-cell antibodies ; and ultimately 5) blockade of effector functions, e.g. with the use of monoclonal antibodies against cytokines, chemokines, and /or adhesion molecules (reviews : 9,10).

Treatment of the donor with either antioxidants or TLR4 antagonists might already be commenced before documentation of brain death, however, with another

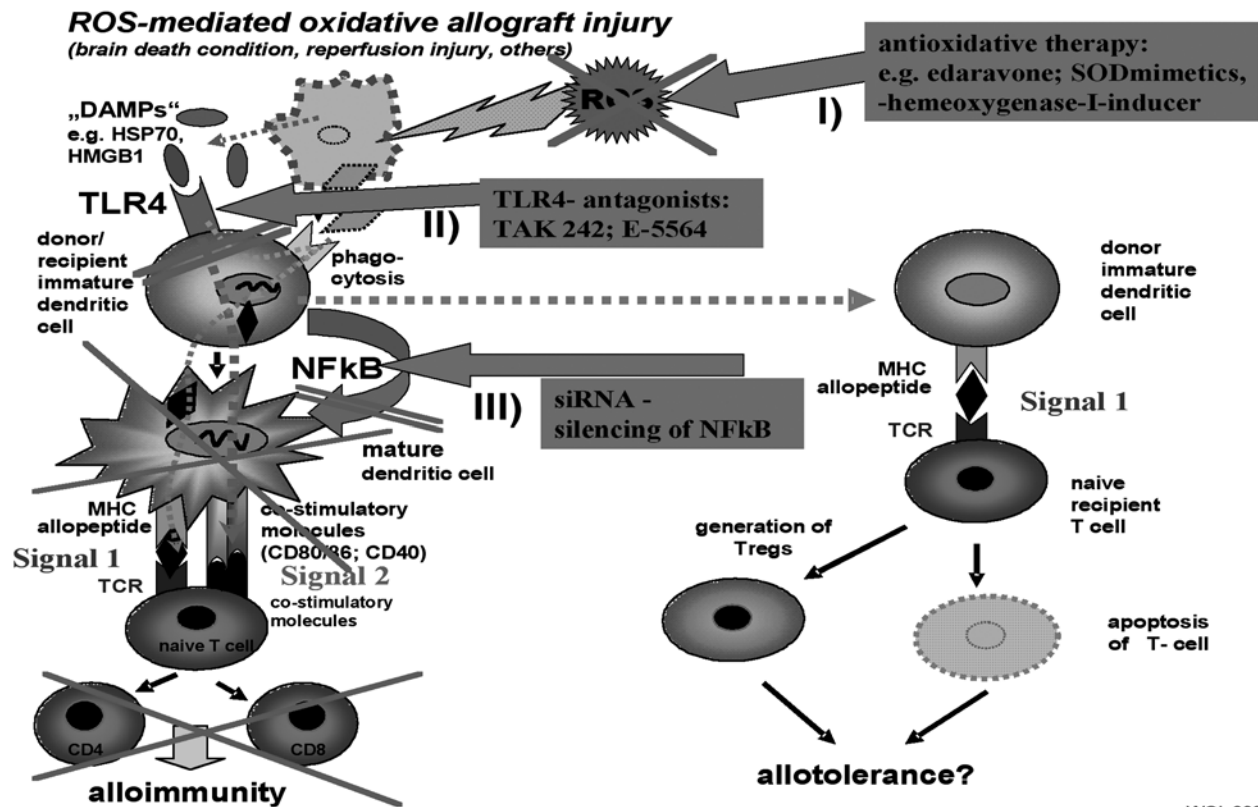


Fig. 2

Schematic illustration of some innate alloimmunity-suppressing strategies : Main aim : to prevent oxidative injury-induced, TLR4-triggered, NFκB-mediated maturation of donor-derived and recipient-derived dendritic cells-resulting in insufficient direct and indirect allorecognition/alloactivation.

I) minimization of the ROS-mediated oxidative allograft injury via antioxidative therapy of both the donor and the recipient during surgery (agents such as edaravone, SOD-mimetica) ;

II) blockade of TLR4 through TLR4 antagonists (E-5564 ; TAK 242) ;

III) generation of immature dendritic cells via siRNA-mediated NFκB-gene silencing followed by their administration to the recipient prior to allografting (see also ref. 20).

indication : reduction/prevention of cerebral oedema. Notably, antioxidative drugs such as edaravone have successfully been used for this indication in patients suffering from acute brain infarction (11). Moreover, recent experiments in mice have shown that cerebral reperfusion injury is mediated by TLR4 (12), suggesting the conduction of clinical trials with TLR4 antagonists in patients with cerebral trauma.

3. Direct/indirect evidence for a beneficial effect of innate-immune-event-suppressing drugs on allograft survival (or other indications)

Notably, every allograft is a reperfused organ and the reperfusion injury leads to activation of the innate immune system. Consequently, mitigation of the reperfusion injury and/or interference with injury-induced innate signalling pathways in DCs should lead to a reduction of allograft rejection. In fact, some direct/indi-

rect evidence in support of this notion has already been reported.

In 1994, first clinical evidence has been published from a clinical trial in kidney transplanted patients using the antioxidative free radical scavenger superoxide dismutase (SOD) : application of SOD during surgery resulted in a significant reduction in incidences of both acute and chronic rejection events (13). In a recently conducted clinical trial in lung transplanted patients, TP-10, a soluble complement–receptor-1 inhibitor, which inhibits the (reperfusion- induced) activation of the complement system by inactivating C3a and C5a convertases, has been shown to exert a beneficial effect by reducing pulmonary ischemia-reperfusion injury (14). In this context, the beneficial effect of pre-transplant / intra-operatively administered polyclonal ATG on allograft survival may be worthwhile to mention (15). This effect may be explained by assuming intragraft elimination of reperfusion injury-induced invasion of innate lymphocytes capa-

ble to trigger DC maturation. Plausibly, additional treatment of the donor with ATG during organ removal should increase this beneficial effect.

As reviewed (10), a large list of powerful antioxidative agents has been published which appear suitable to be tested in future clinical transplant trials, among them edaravone and SOD-mimetics (16, 17). Recent reports of experimental data from preventing the reperfusion injury with the use of small interfering RNA (siRNA), in order to silence the caspase 3 - and caspase 8 genes, are promising and may announce the start of future clinical trials harnessing the phenomenon of RNA interference (18). In view of the fact that the Nobel Prize for Medicine and Physiology in 2006 was given to A.Z. Fire and C.C Mello for their discovery of the RNA interference in 1998 (19), an increasing popularity of this therapeutic modality to inhibit events of innate immunity can be expected.

Indirect support for a successful outcome of this therapeutic concept comes from recent experiments in which donor-innate TLR-triggered signalling pathways, leading to transcriptional gene expression, were disrupted by deletion of the adaptor molecules MyD88 and TRIF or by silencing the NF κ B gene, respectively. Using donor mice with simultaneous deletions of the adapter proteins MyD88 and TRIF, it was demonstrated that absence of both MyD88 and TRIF adapter proteins in the donor species prolonged skin allograft survival, notably across a complete MHC and minor antigen barrier (20). Another experiment demonstrated permanent survival of/successful tolerance induction to murine heart allografts, associated with the generation of Tregs, as a consequence of previous application of allogeneic tolerogenic iDCs (achieved by using siRNA- induced gene silencing of the NF κ B family member RelB in cultured donor-derived DCs) (21).

In regard to other non-transplant indications, the antioxidative drug edaravone, registered in Japan as "Radicut", is successfully administered to patients with cerebral stroke (11). In addition, first clinical evidence of a beneficial effect of other innate immune event-suppressing drugs has been shown in ongoing trials : 1) in patients suffering from severe sepsis with the use of TLR4-antagonists (E-5564) (22), and 2) in patients with acute myocardial infarction or undergoing coronary artery bypass surgery with the use of Pexelizumab (moAB against complement fragment C5) (23).

4. Advantages of a successful use of innate alloimmunity-suppressing drugs in transplant patients call for their clinical development

According to recent growing evidence from reports in the international literature, one can assume that successfully applied therapeutic modalities in suppressing intra-

graft innate immune events result in either subsequent significant reduction in, or only transitory administration of, or even complete avoidance of immunosuppressive therapy associated with improvement of short-term and long-term allograft outcomes and/or drastic reduction in incidences of life-threatening infectious, malignant, and cardiovascular diseases. In its optimal sense, successful drug-mediated suppression of intragraft innate immune events may even culminate in successful clinical allotolerance induction. Altogether, such outcomes would drastically reduce the overall costs associated with organ transplantation today.

In the light of the encouraging clinical and experimental data, clinical trials with the use of innate alloimmunity-suppressing drugs are urgently warranted, e.g. with the use of antioxidative drugs such as SOD-mimetics, edaravone, and hemeoxygenase I-inducers ; with application of polyclonal ATG to the brain dead donor ; with the use of TLR4-antagonists and/or complement fragment inhibitors ; and with the use of siRNA against molecules of interest such as NF κ B. One would expect that planning of the design and conduction of such trials are already on the way - but this is wide of the mark ! In contrary, a considerable reluctance of the pharmaceutical industry to fund the development of such agents/treatment modalities can currently be noticed.

5. Hurdles on the level of pharmaceutical companies to develop innate alloimmunity-suppressing drugs

Several quite legitimate reasons for not developing innate alloimmunity-suppressing drugs are presented by representatives of the pharmaceutical industry. Today's Research & Development (R&D)-based pharmaceutical industry (in particular the large companies currently involved in the production of immunosuppressive drugs in the field of organ transplantation) are reluctant to invest in the high cost of clinical development of drugs because there are no marketing interests, that is to say, because return on investment cannot be guaranteed in view of an only one-week-treatment period : Time-limited treatment of early innate immune events in the donor and the recipient does not represent a profitable market. This scenario may be compared with a quite similar problem encountered in the field of both the development of drugs for neglected diseases (infectious diseases of the poor in developing tropical and subtropical areas) (24) and development of drugs for rare conditions (orphan drugs) (25). In fact : With the emergence of a free market-based world order, profit prospects rather than global health needs guide the direction of new drug development. Even more critical is the problem observed in the field of organ transplantation : Successful treatment of allograft injury may lead to drastic reduction of the long-term administration of

drugs for the suppression of the subsequent ongoing adaptive alloimmune response or may even result in successful allotolerance induction – a fact which may destroy the business of those companies currently involved in the production of effective and powerful immunosuppressive drugs.

But there are other legitimate reasons of the “Big Pharma” not to develop novel agents for the treatment of transplant patients such as the recognition that the conduction of large clinical trials associated with subsequent drug approval is becoming increasingly problematic.

Regulatory authorities have come under increasing public and government scrutiny particularly in making decisions regarding the safety of novel agents in all therapeutic areas. In the organ transplantation arena, the example of the promising immunosuppressive drug “FTY 720” is striking in which infrequent eye toxicity (macula oedema) was not observed until after the development of the drug had already reached phase III trials. Consequently, the development of “FTY 720”, at least in the field of organ transplantation, had to be discontinued at this point. Obviously, these scenarios seem to be a plausible and legitimate explanation for the maintenance of companies’ reluctances although this kind of argumentation has also been critically questioned (26). On the other hand, smaller pharmaceutical companies which have recently discovered useful drugs, e.g. certain siRNAs of interest, and which are potentially able to develop them, do not have the financial power to design and perform clinical trials on their own. The motivation to continue their efforts may be grounded on some hope that the Big Pharma will ultimately buy their innovative agents once proven to be extremely effective and to promise a big market.

6. Hurdles on the level of the transplant community to encourage the development of innate alloimmunity-suppressing drugs

Mobilizing existing expertise and knowledge within the international transplant community to address the specific needs of developing new innovative drugs for transplant patients will require the establishment and wide dissemination of an essential R&D agenda. This agenda should list and prioritize the needs and, particularly, should specify possible transplantation-specific factors that need to be taken into account, such as the recent discovery of innate immunity and its consequences for organ transplantation, potential advantages of innate alloimmunity –suppressing drugs as well as the risks, complications and the immense costs associated with the currently used long-term administration of immunosuppressive drugs. However, there are problematic hurdles again : 1) the transplant community is just begin-

ning to get aware of the new field of innate alloimmunity at all ; 2) the large pharmaceutical companies continue to offer investigator-driven clinical trials with the use of the currently registered immunosuppressive drugs, for example, to convert patients to their own drug, e.g. for reasons of less efficiency or intolerance of the competitor’s drug ; for example, to design studies with other immunosuppressive protocols but by maintaining their own product in this new protocol. Participation in those trials has a lot of advantages for transplant clinicians : funding of their research work, invitation to deliver lectures worldwide and to write overviews in transplant journals (plus provision of an honorarium) ; invitation to attend international congresses free of charge, etc. Consequently, the transplant community – perhaps unconsciously - may be more interested in continuing participation in those clinical trials instead of calling for trials with new innate alloimmunity-suppressing drugs. At least at the end of 2007, there was no voice of any transplant society worldwide to be heard in this regard.

7. Who should fund ?

In view of the considerable reluctance of the pharmaceutical industry to fund the development of innate alloimmunity-suppressing agents, the ethical question has to be raised : “who should fund” ? In principle, responsibilities of funding the development of new drugs have to be sought not only on the level of private pharmaceutical companies, but also on the level of the transplant community and the public. Some of the solutions discussed below call for changes in public/ social/governmental policies and are going to come at some cost. Quite simply, if we want new immunosuppressive therapies, then someone is going to have to pay for it and, thus, we have to seek for modalities under which such a payment can be realized : e.g. to provide incentives to the “Big Pharma” companies ; to install scenarios in which the costs of clinical trials can be reduced ; to create public-private partnerships in which the burden of the development is shared between institutions and organisations. Some of those modalities will be explored in the following by emphasizing possible solutions which may be tackled and perhaps be realized under the auspices and the sponsorship of European organisations, e.g. the European Union, the Council of Europe, and the European Science Foundation. The ELAP platform may turn out to act as an ideal link between these organisations and may provide a forum to efficiently start European initiatives.

8. Exploration of Possible Solutions

Today, the position of the pharmaceutical industry in a highly competitive global market place has turned drugs

from a public health tool into a commodity. It is clear that if the decision to invest in R&D is based purely on economic terms, there is virtually no chance that innate alloimmunity-suppressing drugs will be developed. Clearly, development of additional drugs in transplant medicine requires a different framework. It is the role and duty of national governments and international bodies, such as the EU, to place global health needs high on the international political agenda. But this requires a priori information about those needs by the professional group concerned, a political will, as well as a strong commitment to place health considerations above economic interests. In our case, this implies to enforce rules, regulations and other mechanisms to stimulate innovative drug development for transplant patients. An urgent reorientation of policy, e.g. on the level of EU, is warranted. It is essential that the pharmaceutical industry contributes to the search for solutions, both at a national and international level. But industry alone cannot set the rules of the game. 50 years after the foundation of the EU and in view of the ongoing process of creating a new European Order, the global economy must be structured to address the true needs of society and this includes the needs of thousands of patients to be transplanted in the near future. In this context, three major categories of actions should be considered here.

a) *Provision of Incentives to Companies*

Facilitation of protection of intellectual property : Inventions, such as a new drug or its manufacturing process, can be protected through patenting. A patent gives the owner the right to restrain others from producing and selling the patented product for a given period in any country where the patent has been granted. Promising and extending market exclusivity could be an incentive, e.g. provided by strengthening and broadening of patent protection. Notably, however : while the pharmaceutical industry argues in favour of such a strengthening and broadening of patent protection as a stimulus for R&D, there are growing complaints from within the scientific community that patents can become a barrier to medical progress. Patents in science promote secrecy and strongly hinder free information exchange between researchers, yet this is the basis for scientific progress (27, 28).

Improvement of legal and regulatory environment : The growing strict and complex regulations that dominate the development and sale of new drugs contribute to the high costs and time-consuming nature of drug development. Although a strict and strong regulatory framework is mandatory to protect the health of patients, legal and regulatory excesses may hinder development of and access to drugs. There may be also regulatory barriers to develop innate alloimmunity-suppressing drugs which

may prevent companies from starting such an adventure. Insistence on compliance with such demanding excessive regulations further increases the development costs and creates a major disincentive to small companies from developing countries or emerging markets trying to enter the market. Perhaps a less costly solution would be to make the development of those drugs less expensive by allowing for smaller sized clinical trials coupled with faster and easier regulatory approvals. The fact that all the prevailing trends are in the opposite direction demonstrates why more and more companies are exiting this field.

Creation of an European regulatory framework : To overcome legal and regulatory barriers towards drug development for transplant patients, an adapted European legislative and regulatory framework should be created. What we need, for example, is a legal framework of a regulation of those innate alloimmunity-suppressing drugs in analogy to orphan drug regulations which have been implemented in Europe in 1999/2000 ("EU Regulation on Orphan Medicinal Products Regulation (EC) 141/2000"- approved by the EU on 16.12.1999 and entered into force on the day of its publication in the Official Journal of the European Communities on 22.01.2000) (29). The regulation encourages development of drugs for diseases affecting less than 5 out of every 10,000 of the EU population. The purpose of this regulation is to introduce incentives to develop and market medicinal products for the prevention, diagnosis and cure of rare conditions. Laid in these regulations, financial incentives include a 10-year period of market exclusivity/monopoly and exemptions from market-approval fees. In Europe, only four years after implementation of the Regulation, 271 products have been designated and 18 products have received marketing authorization. Moreover, several biotechnology firms have been created to develop treatments for rare diseases (30).

b) *Conduction of clinical trials in developing countries*

Another issue is the consideration about conducting clinical trials in low-income developing countries among which a strong desire exists to link up with western institutions at any costs. In fact, transplant centres working under high clinical standards and performing a high annual rate of kidney transplantations can be found in developing countries such as India, Pakistan, and Brazil. High development costs could be reduced if the trials would be performed in those transplant centres. Less bureaucratic paper work should allow those trials to be performed in a shorter period of time-which could translate into saving even more money. Nevertheless, there is a variety of crucial ethical issues associated with the conduction of clinical trials in developing countries

(including injustice of the use of placebo control groups, coerciveness of the offer to participate, exploitation of Third World countries in general, etc.) which will not be dealt with in this article (31, 32). At any rate, all those trials, if realized, must be carried out in accordance with the ethical principles laid down in the current revision of the Declaration of Helsinki. Operational research and new studies on existing drugs can already be conducted in developing countries, why not clinical studies with new drugs? This could include the establishment of optimal and modern treatment protocols for transplant patients. As a matter of fact, transplant patients in developing countries may profit from trials with innate alloimmunity-suppressing drugs: In case of successful trial outcomes, subsequent reduction in immunosuppression implies a cheaper therapy and may become affordable for more patients in these low-income countries.

Interestingly enough, an official European-Developing Countries Clinical Trials Programme (EDCTP) has already been established (33). This partnership is a new venture between 14 states of the European Union and Norway to support the conduct of clinical trials of drugs and vaccines (and microbicides) against HIV/AIDS, malaria and tuberculosis in Africa, to develop the capacity to conduct such trials in African institutions, and to promote a more integrated approach to health research amongst European countries. It is funded for 5 years with a contribution of Euros 200 million from the European Commission, matched by an equivalent sum that is spent directly by national research programmes of EU member states and Norway on activities that fall under the EDCTP remit.

c) *Creation of a Public-Private-Transplant Professional Partnership*

As outlined above, dedicated money is needed to enable the development of new innate alloimmunity-suppressing drugs for transplant patients. Another approach to a satisfying solution of this problem will require persuasive re-prioritizing of budget allocations by all involved players outside of the pharmaceutical industry. Public – private professional partnerships that combine engagement, finance and expertise from both sectors in addressing public health priorities should be encouraged (34). Those partnerships, which will bring together pharmaceutical companies, academic transplant professionals, not-for-profit organizations, traditional public-sector organizations, philanthropists, governmental and inter-governmental agencies, are an increasingly popular solution. A workshop on that topic has recently been organized in France entitled “public-private partnership models in Europe-comparison between France and European countries” (35). These partnerships result in a complementarity of skills and resources that can accelerate the

development and delivery of innate alloimmunity-suppressing drugs. Private foundations must also participate in this effort, while the pharmaceutical industry should be stimulated or directed to invest in drug development that responds to global health needs. Given that governments are granting the pharmaceutical industry a monopoly on the market for therapeutic agents, governments could in return demand that a small percentage of profits go towards developing essential drugs which does not reflect marketing interests. Foundations could be established to fund research and development activities in accordance with the priorities defined in the R&D agenda of innate alloimmunity and its suppression. If, in the future, there is still no market, centralized purchases may be recommended. For example European Organ Procurement Organisations may purchase a drug which has proven efficacy in suppressing the innate immune system of brain dead donors. European Transplant Centres may do the same to treat the innate immune system of the recipient during organ transplantation.

Notably, such a partnership similar to that as outlined here, has already been established by the European Union: the “European Rare Diseases Therapeutic Initiative” (ERDITI) (30). ERDITI is an innovative partnership between ~10 European academic institutions and 4 pharmaceutical companies (Aventis-Sanofi, GlaxoSmithKline, Roche, and Servier) established to develop drugs for the treatment of rare diseases and to facilitate the evaluation of compounds that have been or are being developed by pharmaceutical companies. ERDITI is sponsored by the European Science Foundation and is coordinated by the French Institute for Rare Diseases Research.

d) *Outlook and Recommendation: Creation of a new partnership: “The European Initiative for the Suppression of Innate Alloimmunity” (“EISIA”)*

In analogy to ERDITI, the creation of a Public-Private - Transplant Professional Partnership is suggested and recommended by the authors in order to promote therapeutic research and development of drugs for suppression of innate alloimmune events. Such a partnership may be called: “The European Initiative for the Suppression of Innate Alloimmunity” (EISIA).

European Transplant Centres, European Organ Procurement Agencies, European Academic Research Institutions, and pharmaceutical companies are encouraged to establish an innovative partnership to facilitate the evaluation of compounds that have been, are being, or will be developed by pharmaceutical companies. This partnership should be sponsored by ELPAT in terms of a link with the European organisations, e.g. EU, Council of Europe, as well as coordinated by ESOT.

In analogy to the goals of ERDITI, the 3 main goals of EISIA should be (Table I):

Table I

Recommendation for a public-private partnership :
Creation of "The European Initiative for the Suppression of
Innate Alloimmunity" (EISIA) – and its three main goals

Main goals : EISIA

- to provide a streamlined facilitated process of collaboration between academic teams / transplant centres and pharmaceutical companies to develop innate alloimmunity-suppressing drugs ;
 - to give academic teams / transplant centres facilitated access to a large variety of compounds developed by companies for other indications which can be evaluated preclinically in a transplant setting, and, if warranted, clinically ;
 - to guarantee the continuity all the way from research to development and commercialisation of the drug. If preclinical studies uncover the potential of a compound for suppressing innate alloimmune events, the Pharma Partner who has rights to this compound will either develop himself the drug for organ transplantation indication or allow its development by the academic team or a third party if he has no intentions of developing himself.
- to provide a streamlined facilitated process of collaboration between Academic Teams / Transplant Centres, Multicentre Study Groups, and Pharma Companies to develop innate alloimmunity-suppressing drugs ;
- to give Academic Teams / Transplant Centres / Multicentre Study Groups (such as the EUROSPK-Study Group) facilitated access to a large variety of compounds, developed by companies for other indications, which can be evaluated pre-clinically and, if warranted, clinically ;
- to guarantee the continuity all the way from research to development and commercialisation of the drug. If preclinical studies uncover the potential of a compound for suppressing innate alloimmune events, the Pharma Partner who has rights to this compound will either develop himself the drug for organ transplantation indication or allow its development by the Academic Team, a Multicentre Study Group or a Third Party if he has no intentions of developing himself.

To ensure the success of this public-private partnership, a Steering Committee of dedicated transplant professionals has to be established first which should seek for intense contacts with the industrial partners on one hand and responsible authorities of the European Organisations (e.g. EU, Council of Europe) on the other hand. At the European level, the challenge for such a Steering Committee will be to establish and fund a competent platform, such as the ELPAT platform. This platform should predominantly achieve two issues : (1) the ability to identify and fund promising preclinical /clinical projects, and (2) the development of multicentered projects through the provision of necessary expertise and funding.

References

1. AKIRA S. TLR-signaling. *Curr Top Microbiol Immunol*, 2006, **311** : 1.
2. MUNZ Ch., STEINMAN R. M., FUJII S.-I. Dendritic cell maturation by innate lymphocytes : coordinated stimulation of innate and adaptive immunity. *J Ex Med*, 2005, **202** : 203.
3. JAYASEKERA J. P., MOSEMAN E. A., CARROLL M. C. Natural antibody and complement mediate neutralization of influenza virus in the absence of prior immunity. *J Virol*, 2007, **81** : 3487.
4. LAND W. G. The role of postischemic reperfusion injury and other nonantigen-dependent inflammatory pathways in transplantation. *Transplantation*, 2005, **79** : 505.
5. MAHNKE K., ENK A. H. Dendritic cells : key cells for the induction of regulatory T cells ? *Curr Top Microbiol Immunol*, 2005, **293** : 133.
6. TAN P. H., SAGOO P, CHAN C. *et al.* Inhibition of NF-kappa B and oxidative pathways in human dendritic cells by antioxidative vitamins generates regulatory T cells. *J Immunol*, 2005, **174** : 7633.
7. WALSH M. C., BOURCIER T., TAKAHASHI K. *et al.* Mannose-binding lectin is a regulator of inflammation that accompanies myocardial ischemia and reperfusion injury. *J Immunol*, 2005, **175** : 541.
8. ZHANG M., AUSTEN W. G. Jr., CHIU I. *et al.* Identification of a specific self-reactive IgM antibody that initiates intestinal ischemia / reperfusion injury. *Proc Natl Acad Sci USA*, 2004, **101** : 3886.
9. LAND W. G. Immunosuppressive strategies in organ transplantation in the light of innate immunity. *Exp Clin Transplant*, 2006, **4** : 406.
10. LAND W. G. Innate immunity mediated allograft rejection and strategies to prevent it. *Transplant Proc*, 2007, **39** : 667.
11. EDARAVONE ACUTE INFARCTION STUDY GROUP. Effect of a novel free radical scavenger, edaravone (MCI-186), on acute brain infarction. Randomized, placebo-controlled, double-blind study at multicenters. *Cerebrovasc Dis*, 2003, **15** : 222.
12. CAO C. X., YANG Q. W., LV F. L., *et al.* Reduced cerebral ischemia-reperfusion injury in Toll-like receptor 4 deficient mice. *Biochem Biophys Res Comm*, 2007, **353** : 509.
13. LAND W., SCHNEEBERGER H., SCHLEIBNER S. *et al.* The beneficial effect of human recombinant superoxide dismutase on acute and chronic rejection events in recipients of cadaveric renal transplants. *Transplantation*, 1994, **57** : 211.
14. KESHAVJEE S., DAVIS R. D., ZAMORA M. R. *et al.* A randomized, placebo-controlled trial of complement inhibition in ischemia-reperfusion injury after lung transplantation in human beings. *J Thorac Cardiovasc Surg*, 2005, **129** : 423.
15. KADEN J., STROBELT V., MAY G. Short and long-term results after pretransplant high-dose single ATG-Fresenius bolus in cadaveric kidney transplantation. *Transplant Proc*, 1998, **30** : 4011.
16. TAHARA M., NAKAYAMA M., JIN M. B. *et al.* A radical scavenger, edaravone, protects canine kidneys from ischemia-reperfusion injury after 72 hours of cold preservation and autotransplantation. *Transplantation*, 2005, **80** : 213.
17. MASINI E., CUZZOCREA S., MAZZON E. *et al.* Protective effects of M40403, a selective superoxide dismutase mimetic, in myocardial ischaemia and reperfusion injury in vivo. *Br J Pharmacol*, 2002, **136** : 905.
18. ZHANG X., VLADAU C., FENG B. *et al.* Prevention of renal ischemic injury by silencing the expression of renal caspase 3 and caspase 8. WTC-Congress Boston, abstract # 711. *Am J Transplant (Supplement)*, 2006, p. 307.
19. FIRE A., XU S., MONTGOMERY M. K. *et al.* Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*. *Nature*, 1998, **391** : 806.
20. MCKAY D., SHIGEOKA A., RUBINSTEIN M., SURH Ch., SPRENT J. Simultaneous deletion of MyD88 and Trif delays major histocompatibility and minor antigen mismatch allograft rejection. *Eur J Immunol*, 2006, **36** : 1994.
21. LI M., ZHANG X., ZHENG X. *et al.* Immune modulation and tolerance induction by RelB-silenced dendritic cells. WTC-Congress Boston, abstract# 725. *Am J Transplant (Supplement)*, 2006, p. 311.
22. ONDIVEERAN H. K., FOX-ROBICHAUD A. Drug evaluation E-5564. *IDrugs*, 2004, **7** : 582.

23. MAHAFFEY K. W., VAN DE WERF F., SHERNAN S. K. *et al.* Effect of pexelizumab on mortality in patients with acute myocardial infarction or undergoing coronary artery bypass surgery : a systemic overview. *Am Heart J*, 2006, **152** : 291.
24. TROUILLER P., TORREELE E., OLLIARO P. *et al.* Drugs for neglected diseases : a failure of the market and a public health failure ? *Trop Med Int Health*, 2001, **6** : 945.
25. WASTFELT M., FADEEL B., HENTER J. I. A journey of hope : lessons learned from studies on rare diseases and orphan drugs. *J Intern Med*, 2006, **260** : 1.
26. ANGELL M. Excess in the pharmaceutical industry. *CMAJ*, 2004, **171** : 1451.
27. BARTON J. H., EMANUEL E. J. The patents-based pharmaceutical development process : rationale, problems, and potential reforms. *JAMA*, 2005, **294** : 2075.
28. BOBROW M., THOMAS S. Patents in a genetic age. *Nature*, 2001, **409** : 763.
29. VALVERDE J. L. (Ed). The European Regulation on Orphan Medicinal Products. Vol. 3 : Pharmaceuticals Policy and Law. Amsterdam, The Netherlands : IOS Press, 2001.
30. FISCHER A., BORENSZTEIN P., ROUSSEL C. The European rare diseases therapeutic initiative. *PLoS Med*, 2005, **2** : e243.
31. BRODY B. A. Ethical issues in clinical trials in developing countries. *Stat Med*, 2002, **21** : 2853.
32. HAYASAKA E. Approaches vary for clinical trials in developing countries. *J Natl Cancer Inst*, 2005, **97** : 1401.
33. OLLIARO P., SMITH P. G. The European and developing countries clinical trials partnership. *J HIV Ther*, 2004, **9** : 53.
34. WHEELER C., BERKLEY S. Initial lessons from public-private partnerships in drug and vaccine development. *Bull World Health Organ*, 2001, **79** : 728.
35. DEMOTES-MAINARD J., CANET E., SEGARD L. Public-private partnership models in France and in Europe. *Therapie*, 2006, **61** : 325-334, 313.

W. G. Land, M.D. Ph.D.
 c/o Baskent University, Ankara, Turkey
 Liaison Office - Germany
 Köglweg 32
 82024 Taufkirchen-München, Germany
 Tel. : + 49 89 666 11 400
 Fax : + 49 89 666 11 673
 Mobile : + 49 171 14 63 792
 E-mail : walterland@aol.com