

World Journal of *Transplantation*

World J Transplant 2012 October 24; 2(5): 69-83





Editorial Board

2011-2015

The *World Journal of Transplantation* Editorial Board consists of 100 members, representing a team of worldwide experts in transplantation. They are from 29 countries, including Argentina (1), Australia (1), Belgium (1), Brazil (6), Canada (1), China (9), Czech Republic (1), France (3), Georgia (1), Germany (4), Greece (2), Hungary (1), India (2), Iran (3), Israel (1), Italy (9), Japan (4), Netherlands (3), Norway (1), Poland (1), Saudi Arabia (2), South Korea (2), Spain (2), Switzerland (1), Tunisia (1), Turkey (4), United Kingdom (7), and United States (26).

EDITOR-IN-CHIEF

Maurizio Salvadori, *Florence*

GUEST EDITORIAL BOARD MEMBERS

Yu-Fan Cheng, *Kaohsiung*
Yang-Jen Chiang, *Taoyuan*
Shiaw-Min Hwang, *Hsinchu*
Tang-Her Jaing, *Taoyuan*

MEMBERS OF THE EDITORIAL BOARD



Argentina

Walter Guillermo Douthat, *Cordoba*



Australia

Neil Boudville, *Perth*



Belgium

Olivier Detry, *Liège*



Brazil

Luiz A Alves, *Rio de Janeiro*
Ilka FSF Boin, *Campinas*
Niels Olsen Saraiva Câmara, *Sao Paulo*
Eleazar Chaib, *Sao Paulo*
Renato F da Silva, *São José do Rio Preto*
Katherine A Teixeira de Carvalho, *Curitiba*



Canada

Caigan Du, *Vancouver*



China

Jun He, *Suzhou*
Godfrey Chi-Fung Chan, *Hong Kong*
See Ching Chan, *Hong Kong*
Yan Chen, *Hong Kong*
KL Cheuk, *Hong Kong*



Czech Republic

Vladimir Holan, *Prague*



France

Ignacio Anegon, *Nantes*
Felix Cantarovich, *Paris*
Loïc Fouillard, *Cergy-Pontoise*



Georgia

Archil Boris Chkhotua, *Tbilisi*



Germany

Andres Beiras-Fernandez, *Munich*
Rainer Birck, *Mannheim*
Hassan Dihazi, *Goettingen*
Christoph Eisenbach, *Heidelberg*



Greece

Costas Fourtounas, *Patras*
Evgenios Goussetis, *Athens*



Hungary

Andrea Ferencz, *Budapest*



India

Sanjay Kumar Agarwal, *New Delhi*
Suraksha Agrawal, *Lucknow*



Iran

Parisa Badiie, *Shiraz*
Seyed Mohsen Dehghani, *Shiraz*
Ahad Eshraghian, *Shiraz*



Israel

Assy Nimer, *Safed*



Italy

Gian Luigi Adani, *Udine*
Umberto Baccarani, *Udine*
Alessandro Busca, *Turin*
Cristina Costa, *Turin*
Andrea Giusti, *Genoa*
Paola Gremigni, *Bologna*
Salvatore Gruttadauria, *Palermo*
Alessandro Isidori, *Pesaro*



Japan

Walid Mohamed El Moghazy, *Kyoto*

Yasuhiro Fujino, *Akashi*
Junya Kanda, *Durham*
Hiroshi Kanno, *Saitama*



Netherlands

Michiel GH Betjes, *Rotterdam*
Frank JMF Dor, *Rotterdam*
Irma Joosten, *Nijmegen*



Norway

Lars Lysgaard Gullestad, *Oslo*



Poland

Piotr Czubkowski, *Warsaw*



Saudi Arabia

Ali Al-Ahmari, *Riyadh*
Imran Khalid, *Jeddah*



South Korea

Curie Ahn, *Seoul*
Jong Wook Chang, *Seoul*



Spain

Ruben Ciria, *Cordoba*
Luis Fontana, *Granada*



Switzerland

Andrea De Gottardi, *Berne*



Tunisia

Kais Harzallah, *Tunis*



Turkey

Elvan Caglar Citak, *Mersin*
Emir Baki Denkbaz, *Ankara*
İhsan Ergün, *Ankara*
Murat Kilic, *Izmir*



United Kingdom

Jacob Attah Akoh, *Plymouth*
Atul Bagul, *Leicester*
Ricky Harminder Bhogal, *Birmingham*
Sarah Anne Hosgood, *Leicester*
Stefan Georg Hübscher, *Birmingham*

Alan Jardine, *Glasgow*
Sanjeev Kanoria, *London*



United States

Robert Aris, *Chapel Hill*
Reto M Baertschiger, *Indianapolis*
Gerald Brandacher, *Baltimore*
Joseph F Buell, *New Orleans*
Herman S Cheung, *Coral Gables*
Diane M Cibrik, *Ann Arbor*
Ari Cohen, *New Orleans*
David KC Cooper, *Pittsburgh*
Cataldo Doria, *Philadelphia*
Amrita Dosanjh, *San Diego*
Stavros G Drakos, *Salt Lake City*
Sukru Emre, *New Haven*
Sherif S Farag, *Indianapolis*
Tibor Fulop, *Jackson*
G Ian Gallicano, *Washington*
Wenda Gao, *Boston*
W Scott Goebel, *Indianapolis*
Rujun Gong, *Providence*
Chad R Gordon, *Baltimore*
Angelika C Gruessner, *Tucson*
Jeffrey B Halldorson, *Seattle*
Mehdi Hamadani, *Morgantown*
Karen Hardinger, *Kansas City*
Ibtesam A Hilmi, *Pittsburgh*
Randeep Kashyap, *Rochester*
Tatsuo Kawai, *Boston*



Contents

Bimonthly Volume 2 Number 5 October 24, 2012

EDITORIAL

- 69 Donating in good faith or getting into trouble? Religion and organ donation revisited
Oliver M, Ahmed A, Woywodt A

REVIEW

- 74 Antineoplastic effects of mammalian target of rapamycin inhibitors
Salvadori M

Contents

World Journal of Transplantation
Volume 2 Number 5 October 24, 2012

ACKNOWLEDGMENTS I Acknowledgments to reviewers of *World Journal of Transplantation*

APPENDIX I Meetings
I-V Instructions to authors

ABOUT COVER *World Journal of Transplantation* Editorial Board, Alexander Woywodt, MD, FASN, FRCP (Edin), Consultant Nephrologist/Hon. Senior Lecturer, Department of Nephrology, Lancashire Teaching Hospitals NHS Foundation Trust, Preston PR29HT, United Kingdom

AIM AND SCOPE *World Journal of Transplantation* (*World J Transplant*, *WJT*, online ISSN 2220-3230, DOI: 10.5500) is a bimonthly peer-reviewed, online, open-access, journal supported by an editorial board consisting of 100 experts in transplantation from 29 countries.
WJT aims to report rapidly new theories, methods and techniques for prevention, diagnosis, treatment, rehabilitation and nursing in the field of transplantation. *WJT* covers topics concerning organ and tissue donation and preservation; tissue injury, repair, inflammation, and aging; immune recognition, regulation, effector mechanisms, and opportunities for induction of tolerance, thoracic transplantation (heart, lung), abdominal transplantation (kidney, liver, pancreas, islets), transplantation of tissues, cell therapy and islet transplantation, clinical transplantation, experimental transplantation, immunobiology and genomics, xenotransplantation, and transplantation-related traditional medicine, and integrated Chinese and Western medicine. The journal also publishes original articles and reviews that report the results of transplantation-related applied and basic research in fields such as immunology, physiopathology, cell biology, pharmacology, medical genetics, and pharmacology of Chinese herbs.

FLYLEAF I-II Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Yuan Zhou*
Responsible Electronic Editor: *Xiao-Mei Zheng*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Jin-Lei Wang*
Proofing Editorial Office Director: *Jin-Lei Wang*

NAME OF JOURNAL
World Journal of Transplantation

ISSN
ISSN 2220-3230 (online)

LAUNCH DATE
December 24, 2011

FREQUENCY
Bimonthly

EDITING
Editorial Board of *World Journal of Transplantation*
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: wjt@wjgnet.com
<http://www.wjgnet.com>

EDITOR-IN-CHIEF
Maurizio Salvadori, MD, Professor, Renal Unit,

Careggi University Hospital, Viale Pieraccini 18, Florence 50139, Italy

EDITORIAL OFFICE
Jian-Xia Cheng, Director
Jin-Lei Wang, Vice Director
World Journal of Transplantation
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: wjt@wjgnet.com
<http://www.wjgnet.com>

PUBLISHER
Baishideng Publishing Group Co., Limited
Room 1701, 17/F, Henan Building,
No.90 Jaffe Road, Wanchai, Hong Kong, China
Fax: +852-31158812
Telephone: +852-58042046
E-mail: bpgooffice@wjgnet.com
<http://www.wjgnet.com>

PUBLICATION DATE
October 24, 2012

COPYRIGHT
© 2012 Baishideng. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT
All articles published in this journal represent the viewpoints of the authors except where indicated otherwise.

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/2220-3230/g_info_20100722180909.htm.

ONLINE SUBMISSION
<http://www.wjgnet.com/esps/>

Donating in good faith or getting into trouble? Religion and organ donation revisited

Mike Oliver, Aimun Ahmed, Alexander Woywodt

Mike Oliver, Aimun Ahmed, Alexander Woywodt, Department of Nephrology, Lancashire Teaching Hospitals NHS Foundation Trust, Preston PR29HT, United Kingdom

Author contributions: All authors contributed to this paper.

Correspondence to: Dr. Alexander Woywodt, MD, FASN, FRCP (Edin), Consultant Nephrologist/Hon. Senior Lecturer, Department of Nephrology, Lancashire Teaching Hospitals NHS Foundation Trust, Preston PR29HT,

United Kingdom. alex.woywodt@lthtr.nhs.uk

Telephone: +44-1772-524629 Fax: +81-99-2755749

Received: April 6, 2012 Revised: July 11, 2012

Accepted: October 20, 2012

Published online: October 24, 2012

Abstract

There is worldwide shortage of organs for solid-organ transplantation. Many obstacles to deceased and live donation have been described and addressed, such as lack of understanding of the medical process, the issue of the definition of brain death, public awareness of the need for transplants, and many others. However, it is clear that the striking differences in deceased and live donation rates between different countries are only partly explained by these factors and many cultural and social reasons have been invoked to explain these observations. We believe that one obstacle to both deceased and live donation that is less well appreciated is that of religious concerns. Looking at the major faiths and religions worldwide, it is reassuring to see that most of them encourage donation. However, there is also scepticism amongst some of them, often relating to the concept of brain death and/or the processes surrounding death itself. It is worthwhile for transplant teams to be broadly aware of the issues and also to be mindful of resources for counselling. We believe that increased awareness of these issues within the transplant community will enable us to discuss these openly with patients, if they so wish.

Key words: Organ donation; Transplantation; Religion

Peer reviewers: Curie Ahn, MD, PhD, Professor, Division of Nephrology, Director, Transplantation Research Center, Director, Transplantation Research Institute, College of Medicine, Seoul National University, 28 Yongon-Dong, Chongno-Gu, Seoul, 110-744, South Korea; Félix Cantarovich, Professor, Faculty of Medical Sciences, Catholic University of Buenos Aires, 9 rue Parent de Rosan, Paris 75016, France; Niels Olsen Saraiva Camara, Professor, Department of Immunology, Cidade Universitaria, Av Prof Lineu Prestes 1730, Sao Paulo 05508900, Brazil

Oliver M, Ahmed A, Woywodt A. Donating in good faith or getting into trouble? Religion and organ donation revisited. *World J Transplant* 2012; 2(5): 69-73 Available from: URL: <http://www.wjgnet.com/2220-3230/full/v2/i5/69.htm> DOI: <http://dx.doi.org/10.5500/wjt.v2.i5.69>

INTRODUCTION

Chronic shortage of organ donors has led to an ever-increasing disparity between supply and demand. One particularly challenging issue in Europe and the United States is that of organ donation to and from patients from ethnic minorities: Many of these patients carry an above-average risk of developing end stage renal failure^[1]. Unfortunately, this patient group is not only statistically less likely to receive a well matched organ on the deceased waiting list but also less likely to volunteer as live donors^[2]. Such patients with prolonged waiting times may result in them becoming a growing burden on dialysis programs, leading to adverse clinical outcomes. Others have previously emphasised that this might also lead to resentment and the temptation into organ trafficking^[3]. We became interested in this topic during our own clinical work serving a varied population in the North West of England. We were intrigued by the fact that a substantial number of patients cited religious concerns as the reason not to go ahead with live donation. We felt that in comparison to other, well described barriers to donation, religious concerns are generally not well appre-

ciated within the transplant community and we sought to explore this issue further. Here, we aim to provide a brief overview of how religious barriers may arise and how the transplant community and society at large might address them in the future.

CHRISTIANITY

Generally, there is a widespread belief amongst the Christian faith that organ donation is a worthwhile act of altruism although the decisions that accompany this should be left to an individual^[4]. As far as we can gather, most Christian faiths are therefore openly supportive or at give their tacit approval. As for Catholicism, we know that the current Pope Benedict XVI is an open advocate of organ donation, having had a donor card himself^[5] ever since the 1970s. Interestingly, it has recently transpired that his decision to donate may be merely theoretical, since Vatican officials say that after a Pope dies, his body must be buried intact^[6]. The Church of England has even gone so far as to declare organ donation a Christian duty^[4]. Some small Christian sub-groups have taken this idea even further to actively promote and expect altruistic donation amongst their followers^[7].

JEHOVAH'S WITNESSES

Jehovah's witnesses are a group of Christian denomination distinct from mainstream Christianity. The idea that Jehovah's witnesses will not accept blood products obviously complicates the issue of transplantation greatly^[8]. Cellsaver techniques, in which the patient's own blood is re-infused during a procedure, are allowed, but transfusion of a pre-surgically donated unit of blood is not^[9]. In the 1960s, this religious group issued statements declaring transplantation as cannibalistic. This view was only revisited and essentially rescinded in the 1980s^[10]. Current views leave the decision to the individual, provided that no blood is transplanted. Consequently there have only been small case series in this patient group^[11]. Some transplant centres require patients to allow emergency transfusion and some authors have proposed that such contracts should be mandatory before transplantation^[11].

This scenario is ethically complex and its discussion is clearly beyond the scope of our little comment. Clearly, such contracts can be seen as coercion. Transplant centres should be encouraged to have an open and honest discussion within the team on this topic to see whether they are prepared, or not, to accept the increased risk with, for example, renal transplantation without the option for rescue transfusion. We believe that it would be difficult to categorically deny Jehovah's witnesses the option of transplantation, as long as their medical team accepts the increased risk and provided that all options and risks have been openly discussed. We would also argue that this situation is not fundamentally different from a transplant centre accepting other high risk transplant candidates.

ISLAM

Whosoever saves the life of one person, it would be as if he saved the life of all mankind. This Qur'an passage highlights a key principle of Islam. The converse of this is that violating the human body is strictly forbidden in Islam. These contradictions have been discussed repeatedly by Islam scholars. In 1996 the United Kingdom Muslim Law Council ruled that organ transplantation is entirely in keeping with Islam^[12] and other, similarly proactive declarations have emerged elsewhere. Nonetheless, and despite repeated attempts by Islam scholars to promote organ donation, many individual Muslims are still reluctant to accept the concept, particularly deceased donation^[13]. As of today, most transplants in predominantly Muslim countries are therefore live donations although it is not clear whether this is solely due to religious concerns. Logistical problems are also highly prevalent in many of these countries and they, too, impede the establishment of national systems for deceased donation. It is also worthwhile to note that there are nuances as to the views taken by Muslims in different countries. Indo-Asian Muslims, for example, seem to be more reluctant to accept deceased donation than Muslims from Arab countries^[10]. It is worthwhile to note that religious concerns are equally important in Muslims living in Western countries: A recent survey confirmed this and reported that only 39% of Western Muslims surveyed felt that organ donation is in keeping with Islam^[3].

JUDAISM

Traditionally, when a member of the Jewish faith dies, burial should take place within 24 h and should never be delayed. Desecration of the cadaver, for what ever reason is frowned upon as is the 'receiving of any benefit from the dead'^[14]. As with other religions, the definition of brain death is particularly problematic in that the traditional Jewish definition of death requires that all brain, respiratory and cardiac output have ceased. Jewish faith also stipulates that organs are treated respectfully^[14]. If an organ is not used at transplantation after removal from the body, it should not simply be discarded.

In Israel, where 75% of the population are of the Jewish faith, only around 10% of the population are in possession of an organ donor card and the deceased donation rate is as low as 9 per million population (2004 data^[10]). The Israeli government has attempted to alleviate the issue with two laws in 2008, firstly to define the time of death and secondly to award a broad range of benefits to live donors. Parts of the ultra-orthodox community have responded to this new law by issuing anti-donation cards^[15]. The cards read: "I do not give my permission to take from me, not in life or in death, any organ or part of my body for any purpose."^[15]

Other religious authorities take a different, proactive view, most notably the Halachic Organ Donor Society (HODS). Uniquely, HODS offers two optional defini-

DONOR DECLARATION

To: ADI—Israel Transplant Center
15 Noah Mozes St, Tel Aviv 67442
Tel: (03) 695-7369, Fax: (03) 695-7344
1-800-609-610

Last Name _____ First Name _____

I.D. No. _____ Year of Birth* _____

Address _____ Town _____ Zip Code _____

Tel. _____ E-mail _____

In order to save another person's life after my death, I hereby bequeath my:

☐ Kidney ☐ Heart ☐ Liver ☐ Lungs ☐ Cornea ☐ Skin

☐ Any organ from which another person may benefit

☐ Under the condition that a religious leader,
chosen by my family, approves the donation

This bequest is for purposes of transplantation only.
*Over 18 only

Date _____ Signature _____

Figure 1 Donor declaration, Israel Transplant Centre, including an optional clause that a religious scholar must be consulted before transplantation can go ahead.

tions of death on their organ donor cards, namely that of brain stem death as well as that of cessation of heart-beat^[14]. HODS has also managed to enlist support of a large number of Rabbis, many of them from orthodox quarters. Their organ donor cards are on display on the HODS website^[16].

Again, uniquely, the Israel Transplant centre allows registered donors to stipulate that a named religious scholar be consulted before donation can go ahead (Figure 1). Some have regarded this clause as highly problematic, given that in Israel preference in the transplant waiting list is given to potential recipients who have signed an organ donor card themselves. Accordingly, people who do not genuinely intend to donate organs would receive preferential treatment as transplant recipients, while in the event of their own death their religious patron could veto donation.

HINDUISM, SIKHISM AND BUDDHISM

The very ethos of Hinduism supports the idea that the physical integrity of the body post-death is not crucial. Hinduism is the predominant religion in South Asia, with around 1 billion followers. Hindus believe in reincarnation as well as any means whereby life can be prolonged or sustained. These principles therefore lend themselves easily to the idea of transplantation^[17] and we are not aware of any particular problems regarding organ donation.

The word Sikh implies learner. The ethos of a Sikh is that religion should be practiced in the living world by dealing with life's day to day problems. Sikhs believe in life after death and a continuous cycle of rebirth. The

physical body is not viewed as important in this process but the idea of doing good actions is^[18]. Again, transplantation is viewed positively amongst the Sikh community.

In Buddhism, the death process is viewed as an important time and some followers are of the opinion that some form of spiritual consciousness remains alive in the body for days after death. These views have led to some contradictions regarding donation from the Buddhist community, mainly surrounding issues with regards to brain stem death diagnosis. These points directly rival the Buddhist ideologies of selflessness and giving to another^[19].

CONFUCIANISM, SHINTOISM AND TAOISM

From the Western point of view it is difficult to say whether Confucianism is a religion as such or an ethical and philosophical system and school of thought. However, mainland China, Taiwan and Korea are countries strongly influenced by the teachings of this important Chinese philosopher. Some teachings of Confucian origin suggest that one is born with a complete body and should die this way^[10]. However, modern Confucians acknowledge that to sustain the life of another is a valued thing. Interestingly, recent data from Korea suggest that there is still some conflict amongst young Koreans as to the appropriateness of transplantation in a Confucian society^[20]. One of the key principles of Confucian society is the deep respect for parents. This could be a factor when family are faced with the decision or not to allow their parent's organs to be donated.

Shinto is the indigenous spirituality of Japan and the people of Japan. Shinto's believe that the body is pure and gathers impurities throughout life. A cadaver is considered very powerful and can impose bad luck if interfered with. Incredibly, organ procurement from "brain dead" donors was only legalized in 1997^[21] and it took another 2 years until in 1999 a heart transplant was performed. Although deceased donation is now legal in Japan, the country continues to have a very low rate of deceased donation. To overcome this problem, Japan developed one of the first ABO incompatible transplant schemes^[22].

Taoism is a philosophical tradition from Eastern Asia whose stance on transplantation essentially revolves around the ethos that changes made to Human form cannot truly affect the essence of life. Organ donation is therefore generally approved.

DISCUSSION

Religious views on organ donation are very diverse, ranging from almost complete opposition (as in the ultra-orthodox Haredim) to profound scepticism (as in parts of the Indo-Asian Muslim community), to a proactive, supporting stance, as in Hinduism or Christianity. Some religious authorities, such as HODS, have found ways to accommodate different views regarding this issue, such as the two-tier organ donor card.

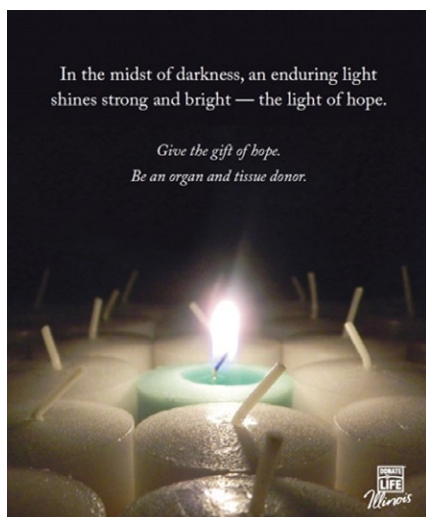


Figure 2 Promotional material for National Donor Sabbath in Illinois, United States. This is part of an organ donation initiative coordinated by Donate Life America, a not-for-profit alliance of national organizations and state teams across the United States committed to increasing organ, eye and tissue donation. Observed on Friday through Sunday two weekends before Thanksgiving, the 3-d period seeks to include the days of worship of major religions practiced in the United States Courtesy of Donate Life Illinois.

We also need to acknowledge that the scriptures around which the different faiths are based do not specifically mention the transplantation of organs. Different scholars and schools of thought within a faith or religion may therefore arrive at different conclusions when interpreting these scriptures. Accordingly, views may differ considerably within one particular faith or between religious scholars and communities. A good example is that of Muslims in Western countries, such as the United Kingdom: Many Muslims in the United Kingdom are not fully aware that the Muslim Law council of Great Britain has explicitly advocated deceased donor transplantation as a means of saving life. The council accepts the medical diagnosis of brain stem death for the purposes of transplantation. The discrepancy between the rulings of Muslim scholars and the views of patients and relatives is clearly evident in our own day-to-day experience in the North-West of England and in recent surveys^[3]. Another good example of different opinions within the spectrum of one faith is Judaism whereby organisations such as HODS take a proactive and to some degree pragmatic view whereas orthodox and ultra-orthodox quarters remain at least deeply sceptical if not opposed.

CONCLUSION

To conclude, we acknowledge that the impact of one's religion on the decision to go ahead with deceased or live donation is perhaps under-recognised. We speculate that religious concerns play a role in many decisions against donation. We find it reassuring that all large world religions approve of organ donation, and that most religious rules and concerns are overcome by the over-arching

principle of altruism. Ideally further education of physicians likely to be faced with these types of dilemmas should be undertaken and new community-based approaches are required to deal with religious concerns in organ donation. Transplant physicians and surgeons need to acquire some knowledge on this topic and Inter-faith initiatives, such as the National Donor Sabbath in the United States^[23] (Figure 2), or the "Wall of Life" initiative in the United Kingdom are particularly welcome.

REFERENCES

- 1 **Feehally J.** Ethnicity and renal replacement therapy. *Blood Purif* 2010; **29**: 125-129
- 2 UK Transplant Activity Report: Kidney. 2009. Accessed July 27, 2010. Available from: URL: <http://www.uktransplant.org.uk/ukt/statistics/statistics.jsp>
- 3 **Sharif A, Jawad H, Nightingale P, Hodson J, Lipkin G, Cockwell P, Ball S, Borrows R.** A quantitative survey of Western Muslim attitudes to solid organ donation. *Transplantation* 2011; **92**: 1108-1114
- 4 Organ donation a Christian duty. Church of England, 2007. Accessed July 15, 2010. Available from: URL: <http://www.cofe.anglican.org/news/pr9607.html>
- 5 **Owen R.** Pope Benedict carries organ donor card as 'an act of love'. 2008. Available from: URL: <http://www.dharma-cafe.com/index.php/news-briefs/article/pope-benedict-carries-organ-donor-card-as-an-act-of-love/>
- 6 The Pope is an organ donor but his body parts cannot be donated. 2011. Available from: URL: <http://www.telegraph.co.uk/news/religion/the-pope/8303510/The-Pope-is-an-organ-donor-but-his-body-parts-cannot-be-donated.html>
- 7 **Truog RD, Lowney J, Hanto D, Caplan A, Brock D.** Soliciting organs on the Internet. *Med Ethics* (Burlingt Mass) 2005; **12**: 5-8
- 8 **Rogers DM, Crookston KP.** The approach to the patient who refuses blood transfusion. *Transfusion* 2006; **46**: 1471-1477
- 9 **Panico ML, Jenq GY, Brewster UC.** When a patient refuses life-saving care: issues raised when treating a Jehovah's Witness. *Am J Kidney Dis* 2011; **58**: 647-653
- 10 **Oliver M, Woywodt A, Ahmed A, Saif I.** Organ donation, transplantation and religion. *Nephrol Dial Transplant* 2011; **26**: 437-444
- 11 **Bramstedt KA.** Transfusion contracts for Jehovah's Witnesses receiving organ transplants: ethical necessity or coercive pact? *J Med Ethics* 2006; **32**: 193-195
- 12 **Golmakani MM, Niknam MH, Hedayat KM.** Transplantation ethics from the Islamic point of view. *Med Sci Monit* 2005; **11**: RA105-RA109
- 13 **Einollahi B.** Cadaveric kidney transplantation in Iran: behind the Middle Eastern countries? *Iran J Kidney Dis* 2008; **2**: 55-56
- 14 Organ Donation and Halacha (brochure): The Halachic Organ Donor Society. Available from: URL: <http://www.hods.org>
- 15 Haredim issue anti-organ-donor cards. Ha'aretz, 2008. Accessed February 19, 2012. Available from: URL: <http://www.haaretz.com/jewish-world/news/haredim-issue-anti-organ-donor-cards-1.251280>
- 16 Hundreds of orthodox rabbis carry organ donor cards. Accessed February 19, 2012. Available from: URL: <http://www.hods.org/English/about/rabbise.asp>
- 17 **NHS Blood and Transplant.** Hindu Dharma and Organ Donation. Accessed July 30, 2010. Available from: URL: http://www.organdonation.nhs.uk/ukt/how_to_become_a_donor/religious_perspectives/leaflets/hindu_dharma_and_organ_d

- onation.jsp
- 18 **Exley C**, Sim J, Reid N, Jackson S, West N. Attitudes and beliefs within the Sikh community regarding organ donation: a pilot study. *Soc Sci Med* 1996; **43**: 23-28
- 19 **Sugunasiri SH**. The Buddhist view concerning the dead body. *Transplant Proc* 1990; **22**: 947-949
- 20 **Kim JR**, Elliott D, Hyde C. The influence of sociocultural factors on organ donation and transplantation in Korea: findings from key informant interviews. *J Transcult Nurs* 2004; **15**: 147-154
- 21 **McConnell JR**. The ambiguity about death in Japan: an ethical implication for organ procurement. *J Med Ethics* 1999; **25**: 322-324
- 22 **Chung CK**, Ng CW, Li JY, Sum KC, Man AH, Chan SP, Cheung JY, Yu KP, Tang BY, Lee PP. Attitudes, knowledge, and actions with regard to organ donation among Hong Kong medical students. *Hong Kong Med J* 2008; **14**: 278-285
- 23 National Donor Sabbath. 2012. Accessed February 19, 2012. Available from: URL: <http://donatelife.net/national-events/>

S- Editor Cheng JX L- Editor A E- Editor Zheng XM

Antineoplastic effects of mammalian target of rapamycin inhibitors

Maurizio Salvadori

Maurizio Salvadori, Renal Unit, Careggi University Hospital, Viale Pieraccini 18, Florence 50139, Italy

Author contributions: Salvadori M solely contributed to this paper.

Correspondence to: Maurizio Salvadori, MD, Professor, Renal Unit, Careggi University Hospital, Viale Pieraccini 18, Florence 50139, Italy. maurizio.salvadori1@gmail.com

Telephone: +39-55-7949269 Fax: +39-55-435878

Received: July 14, 2011 Revised: August 8, 2012

Accepted: October 20, 2012

Published online: October 24, 2012

Abstract

Cancer after transplantation is the third cause of death and one of the more relevant comorbidities. Aim of this review is to verify the role of different pathogenetic mechanisms in cancer development in transplant patients and in general population as well. In particular has been outlined the different role exerted by two different families of drug as calcineurin inhibitor and mammalian target of rapamycin (mTOR) inhibitor. The role of mTOR pathways in cell homeostasis is complex but enough clear. As a consequence the mTOR pathway deregulation is involved in the genesis of several cancers. Hence the relevant role of mTOR inhibitors. The authors review the complex mechanism of action of mTOR inhibitors, not only for what concerns the immune system but also other cells as endothelial, smooth muscle and epithelial cells. The mechanism of action is still now not completely defined and understood. It implies the inhibition of mTOR pathway at different levels, but mainly at level of the phosphorylation of several intracellular kinases that contribute to activate mTOR complex. Many prospective and retrospective studies in transplant patients document the antineoplastic role of mTOR inhibition. More recently mTOR inhibitors proven to be effective in the treatment of some cancers also in general population. Kidney cancers, neuroendocrine tumors and liver cancers seem to

be the most sensitive to these drugs. Best results are obtained with a combination treatment, targeting the mTOR pathway at different levels.

© 2012 Baishideng. All rights reserved.

Key words: Transplant patients; Cancer treatment; Cell proliferation; Mammalian target of rapamycin inhibition; Mammalian target of rapamycin pathway; Protooncogenes; Tumor suppressors

Peer reviewers: Andrea De Gottardi, MD, PhD, Assistant Professor, Clinic of Visceral Surgery and Medicine, Hepatology, Freiburgstrasse, CH-3010 Berne, Inselspital, Switzerland; Caigan Du, PhD, Assistant Professor, Department of Urologic Sciences, University of British Columbia, Jack Bell Research Centre, 2660 Oak Street, Vancouver, BC V6H 3Z6, Canada

Salvadori M. Antineoplastic effects of mammalian target of rapamycin inhibitors. *World J Transplant* 2012; 2(5): 74-83 Available from: URL: <http://www.wjgnet.com/2220-3230/full/v2/i5/74.htm> DOI: <http://dx.doi.org/10.5500/wjt.v2.i5.74>

EPIDEMIOLOGY

Cancer after renal transplantation is one of the main morbidity and is the third cause of death after cardiovascular diseases and infections. Cancers account for 7.5% of deaths of patients with a functioning graft and overall for 15% of deaths after renal transplantation, including patients with non functioning graft.

According to different registries, the prevalence of cancer after renal transplantation with respect to general population is mainly higher for non melanoma skin cancer, bladder, kidney, vulvovaginal cancer and non Hodgkin's lymphoma^[1]. The relative risk of cancer after renal transplantation comparing patients on waiting list is 2.55 for skin cancer, 1.12 for bladder, 1.39 for kidney, 2.19 for vulvovaginal and 3.29 for non Hodgkin lymphoma. The

Australian and New Zealand registry comparing the ratio of observed *vs* expected incidence reports a standardized incidence ratio (excluding nonmelanocytic skin cancer) of 435.6 for vulva, 36.7 for vagina, 26.44 for Kaposi's sarcoma, 10.16 for lymphomas^[2]. Besides conventional risk factors such as advanced age and cigarette smoking, peculiar factors of transplant patients seem to be length of dialysis, chronic viral infections, genetic and immunosuppression^[3]. Table 1 shows the cancers with an incidence after renal transplantation 5-fold higher with respect to general population, compared with cancers that do not show any significant increase. Table 2 shows that the vast majority of malignancies occurring in transplant patients is linked to chronic viral infections also independently from the type of immunosuppressive therapy.

PATHOGENESIS OF MALIGNANCIES IN RENAL TRANSPLANT PATIENTS

Role of different factors in cancer development in transplant patients

The early demonstration of immunological rejection of donor transmitted malignancies after discontinuation of immunosuppressive therapy was the first indication of the role of immunosuppressive therapy in transplant related malignancies. The cancer enhancing role of drugs was further supported by Starzl's report of the regression of lymphomas and lymphoproliferative lesions after the reduction or discontinuation of immunosuppressive drug therapy^[4]. The role of immunosuppression was further amplified by the work of Dantal that prospectively compared the cancer incidence with a low cyclosporine (CsA) regimen with that of a standard dose CsA regimen^[5]. The normal dose group had a significantly higher incidence of any cancer ($P < 0.034$) and of skin cancer ($P < 0.05$). Malignancy-inducing effects of immunosuppressive drugs initially thought to result from drug-induced T-lymphocyte dysfunction i.e., immune surveillance^[6]. As in that period calcineurin inhibitors (CNIs) and in particular CsA represented the cornerstone of immunosuppressive therapy, cancer incidence in transplant patients was thought to be related to immunosuppression and CsA in particular. Later on has been documented that the malignancy-inducing effects may primarily result from direct pro-cancer effects independent of host immune system. These factors include the autonomous proliferation, lack of response to antiproliferative signals, evasion of apoptosis, angiogenesis, tissue invasion and metastasis, replicative immortality. These characteristics may be due to activation of oncogenes or inactivation of cancer suppressor genes that modify regulatory "check points" in cell growth^[7]. Indeed the relationship between immunosuppressive drugs and malignancies is more complex than thought in the past and immune impairment is only one factor, probably not the most relevant in cancer development. Infections, DNA repair, cancer cellular growth and angiogenesis seem to have a relevant role in cancer development in immunosuppressed patients^[8].

Table 1 Cancer risk *vs* general population

Increased ≥ 5 fold	Little/no increase
Skin	Breast
Vulvovaginal	Prostate
Cervix/uterus	Testicular
Lymphoma	Ovarian
Liver	Lung
Kidney/Bladder	Colon

Table 2 Viruses linked to malignancies

Virus	Malignancy
EBV	Lymphoma (PTLD)
HHV-8	Kaposi's sarcoma
HPV	Cervical, vulvar cancer
HPV-58	Bowen disease
HPV 8, 19	Non melanoma skin cancer
HPV 16, 20	Skin and tonsillar carcinoma
HCV, HBV	Hepatocellular carcinoma

EBV: Epstein-Barr virus; HHV: Human herpesvirus; HPV: Human papillomavirus; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

Comparison of CNI vs mammalian target of rapamycin inhibitors in cancer development

As a proof that immunosuppressive agents play only a role, probably not the most important, in cancer development after transplantation is the fact that not all immunosuppressive agents have the same oncogenic activity.

Indeed while in the past the risk of cancer morbidity and mortality has largely been attributed to long-term immunosuppressive drug therapy, which remains necessary to prevent organ allograft rejection, recent studies challenge the premise that all immunosuppressive drugs necessarily promote cancer. A particular class of immunosuppressants referred to as mammalian target of rapamycin (mTOR) inhibitors (mTORIs), has been shown to have potent anti-cancer effects that are now being tested in clinical studies^[9].

The aforementioned Dantal paper documented the pro-oncogenic activity of CNIs as cyclosporine. CNIs may possibly generate cancer growth *via* reduction of lymphocyte response, but more probably by interleukin 6 (IL-6) increase, transforming growth factor β (TGF- β) increase and vascular endothelial growth factor (VEGF) increase (Figure 1).

IL-6 promotes B-cell activation, growth and possibly immortalization. This fact could favour post-transplant lymphoproliferative disorders development.

TGF- β increase mediates phenotypic changes by a cell autonomous mechanism, including invasiveness of nontransformed cells^[10].

CNIs also increase the production of VEGF that is a powerful agent of angiogenesis, strictly linked to cancer cell development and cancer increase^[11]. Indeed CNIs effect on the expression of VEGF leads to an angiogenic milieu that favors cancer growth^[12].

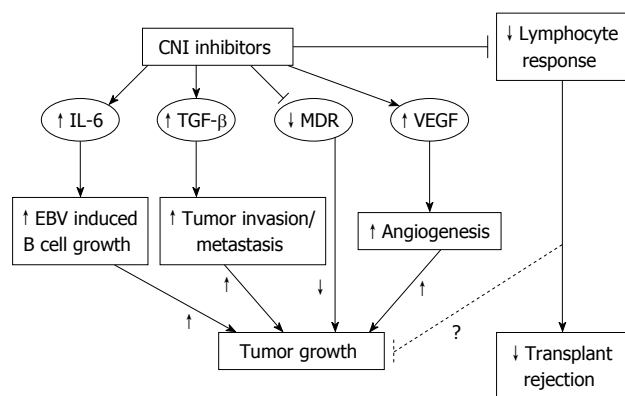


Figure 1 Calcineurin inhibitor and malignancies. CNI: Calcineurin inhibitor; IL: Interleukin; TGF: Transforming growth factor; VEGF: Vascular endothelial growth factor; EBV: Epstein-Barr virus.

The mTORI besides their antirejection effect, seem to have a different profile with respect to malignancies when compared with CNIs.

mTORIs are immunosuppressive agents, widely used in transplantation. They form a complex with the FK binding protein complex (FKBP-12). This complex binds with high affinity to mTOR. Rapamycin and derivatives, including CCI-779 and RAD001, inhibit mTOR, down-regulating p70S6 kinase activity and subsequent translation of specific mRNAs required for cell-cycle progression from the G1 to S phase. In transplantation, everolimus (EVL) and or sirolimus (SRL) demonstrate immunosuppressive properties and has been used to prevent acute rejection in cardiac^[13], liver^[14], lung and renal transplant recipients. It appears that this agent may be potent enough to allow for the minimization or removal of calcineurin inhibitors in the long term of renal transplant recipients.

Due to their action on different kind of cells, besides the action on lymphocytes these drugs have also other effects. Because the action on endothelial and vascular smooth muscle cells in cardiology, EVL is available as a drug-coated stent and is used in percutaneous coronary interventions for prevention of restenosis^[15,16]. Because of the antiproliferative action on fibroblast, rapamycins can cause delay in wound healing and lymphoceles. The same action on fibroblast has also positive effects in liver transplantation, attenuating liver fibrosis^[17,18].

mTORIs could have a protective action against malignancies at least by four different pathways (Figure 2): (1) The increase of E-cadherin levels favors cellular adhesion and blocks neoplastic cells migration^[19]; (2) The increase of p-27kip-1 kinase inhibits cyclins, needed for cell cycle^[20]; (3) The reduction of IL-10 inhibits cellular Janus kinase- Signal transducer and activator of transcription (Jak-Stat) transcription and cell growth^[21]; and (4) The inhibition of the serine-threonine kinase mTOR reduces proliferation of different kind of cells, as (a) Endothelial and smooth muscle cells (angiogenesis); (b) T lymphocytes (antirejection activity); and (c) Neoplastic cells.

Such biological insights on the protective effect of

mTORIs on new malignancies after renal transplantation are confirmed by several retrospective and prospective studies^[22].

The vast majority of these studies compare, as maintenance immunosuppressive therapy, therapies mainly based on CNIs with therapy based on mTORIs without CNIs or with CNIs minimization.

In a randomized prospective trial, patients who received rapamycin-based, calcineurin inhibitor-free therapy after CsA withdrawal at month 3 had a reduced incidence of both skin and non-skin malignancies at 5 years after renal transplantation compared with those who received rapamycin therapy combined with CsA^[23]. In the CONVERT study renal transplant patients were randomized after transplantation either to receive rapamycin or to continue CsA therapy. About 10.2% patients on CNI had malignancies *vs* 3.4% patients converted to rapamycin ($P < 0.001$). The effect was similar for skin cancers (6.9% *vs* 1.8%, $P < 0.001$) and non skin cancers (4.4% *vs* 1.1%; $P = 0.004$)^[24]. In a systematic review and meta-analysis of randomized trials, 33 studies were included (27 trials of SRL, 5 of EVL and 1 head-to-head). The relative risk to have malignancy was lower in any kind of comparison and in favor of mTORIs^[25].

A retrospective study of the OPTN/UNOS database on 33 249 deceased donor kidney transplants revealed that 504 patients received either SRL or EVL without a calcineurin inhibitor, 2321 received either SRL or EVL in combination with a calcineurin inhibitor, and 30 424 received a calcineurin inhibitor without a mTOR inhibitor. Data were censored at 963 d to allow comparable follow up among the treatment groups. The incidence of any malignancy was 0.60% for both SRL/EVL alone and SRL/EVL plus a calcineurin inhibitor and was 1.81% for calcineurin inhibitors ($P < 0.00001$). The incidence rates for *de novo* solid malignancies were 0% for SRL/EVL alone, 0.47% for SRL/EVL plus calcineurin inhibitor, and 1.0% for calcineurin inhibitors. Multivariate analysis indicated that mTOR inhibitor maintenance immunosuppression was associated with a 60% reduced risk of any post-transplant malignancy and a 55% reduced risk of solid malignancy^[26].

mTOR PATHWAY AND CANCER

As aforementioned, rapamycins (a group of parental compounds), block an intracellular serine-threonine kinase called mTOR.

Extracellular signal regulated kinase pathway, c-Jun terminal kinase pathway, p38 pathway and mTOR pathway regulate cell survival, proliferation, apoptosis resistance, angiogenesis and metastasis diffusion^[27]. Therefore is not surprising that such protein deregulation could be involved in cancer development representing a target in the treatment of solid tumors.

Role of mTOR in cell proliferation and cancer development

Which is exactly the role of the serine threonine kinase

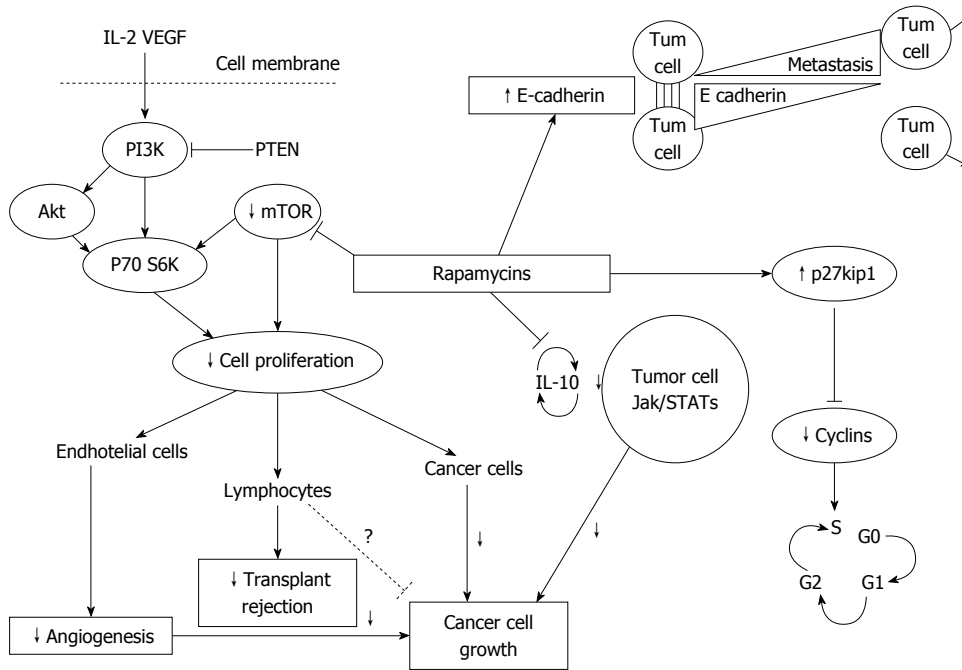


Figure 2 Rapamycins and malignancies. PI3K: Phosphoinositide 3-kinase; mTOR: Mammalian target of rapamycin; IL: Interleukin; VEGF: Vascular endothelial growth factor.

mTOR in cancer development? mTOR is a central controller of cell growth and proliferation in normal cells. mTOR integrates signals from a variety of sources, including nutrients and growth factors. mTOR acts to induce protein synthesis of molecules necessary for angiogenesis^[28], cell growth, and nutrient uptake^[29] for cell survival^[30].

Growth factors, such as insulin like growth factor (IGF), epidermal growth factor (EGF)^[31], platelet derived growth factor, and VEGF, bind to and activate receptors located on the cell surface^[32].

Receptors activate intracellular signaling cascades that regulate cell growth, angiogenesis, and nutrient uptake^[33].

mTOR is a key integration point for information received from upstream receptors^[34].

The mTOR pathway is fully operating in a nutrient rich environment^[35,36]. Indeed the activity of mTOR is regulated by stress-inducing conditions associated to the microenvironment. Suboptimal conditions for cellular anabolic metabolism (e.g., amino acid starvation, hypoxia or glucose deficiency) or cell progression (e.g., growth factor deprivation) inactivate mTOR by several pathways converging on the tuberous sclerosis complex (TSC), which, through its Ras homologue enriched in brain (Rheb-GAP) activity, inactivates Rheb, thereby suppressing mTOR^[37]. Subsequently, energy consumption is reduced through a reduction in protein synthesis, cell delay G1-S progression and cell viability is maintained through autophagic recycling of cellular macromolecules^[24,38].

mTOR pathway and cell proliferation

Figure 3 shows how in normal conditions growth-stimulating signals originating within and outside the cell act

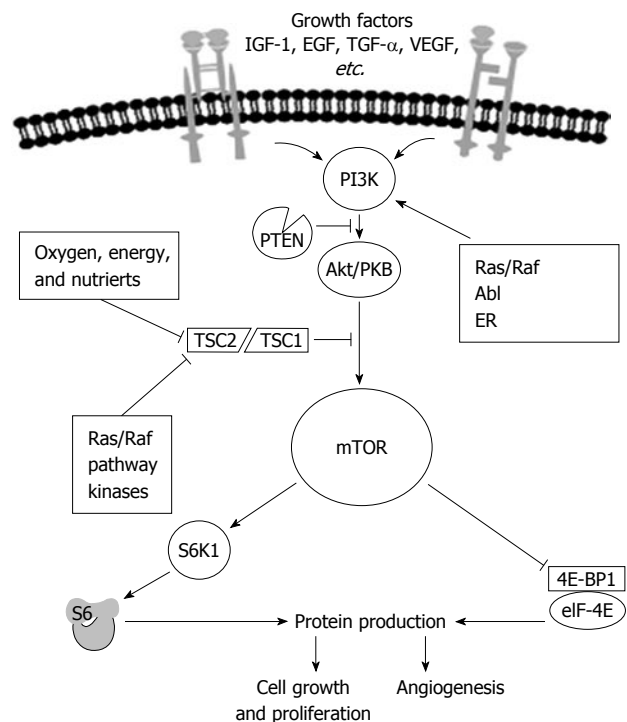


Figure 3 Growth factors and mammalian target of rapamycin pathways. PI3K: Phosphoinositide 3-kinase; mTOR: Mammalian target of rapamycin; IGF: Insulin like growth factor; EGF: Epidermal growth factor; TGF: Transforming growth factor; VEGF: Vascular endothelial growth factor; ER: Estrogen receptor; TSC: Tuberous sclerosis complex.

on growth factor receptors and sequentially on signaling molecules as phosphoinositide 3-kinase (PI3K), that, when not blocked by phosphatase and tensin homologue deleted on chromosome 10 (PTEN), phosphorylates and

activates Akt, that, when not blocked by TSC1/2 activates mTOR.

One of the most interesting recent findings is that mTOR itself is part of two distinct signaling complexes; one complex, mTOR complex 1 (mTORC1) receives a signal from an upstream molecule AKT and is rapamycin sensitive, the second complex, mTOR Complex 2 (mTORC2) regulates AKT through Ser473 phosphorylation, mTORC2 is rapamycin insensitive. AKT is activated by phosphoinositide-dependent kinase 1 (PDK1) phosphorylation at a second site, Thr308, with phosphorylation at both sites required for maximal AKT activity^[39]. Growth factors binding to their cognate receptors results in a recruitment of receptor substrate (e.g., insulin receptor substrate; IRS-1), and binding of PI3K. PI3K converts phosphatidylinositol-4,5-phosphate (PIP2) to phosphatidylinositol-3,4,5-phosphate (PIP3), which recruits PDK1 that phosphorylates AKT in the site Thr308. mTORC2 regulates also AKT through Ser473 phosphorylation. Importantly, phosphatase and tensin homologue deleted on chromosome 10 (PTEN), a tumor suppressor, reverses the PIP2-to-PIP3 reaction, thus reducing AKT activity. When activated, AKT mediates mTORC1 activation *via* inhibition of a tumor suppressor complex made up the two tuberous sclerosis proteins, hamartin (TSC1) and tuberin (TSC2). The TSC1/2 complex functions as a GTPase-activating protein, resulting in inactivation of Ras homolog enriched in brain (Rheb). In the GTP-bound state, Rheb selectively complexes with and activates mTORC1^[40,41].

From another perspective has been recently discovered that inhibitory κ B kinase β , a kinase downstream of tumor necrosis factor α , integrates with mTORC1 by inhibiting TSC1/2, thus providing a new molecular link between inflammation and cancer^[42].

The importance of mTOR in regulating normal cell growth, cell division and angiogenesis is highlighted by the number of proteins involved in its activation or inhibition^[43,44].

mTOR is deregulated in cancer by increased upstream signaling, loss-of-function mutations in upstream inhibitors, and activating mutations in mTOR activators.

Increased mTOR activity results in the increased protein synthesis of more than 100 genes and proteins involved in cellular responses. Many of the proteins that are regulated by mTOR support the growth, metabolic requirements, and survival of cancer cells.

Deregulation of the mTOR-linked pathways increase the risk of developing cancer or have been identified in many cancers^[45,46].

mTOR pathway and angiogenesis

mTOR activation, beside other activities, stimulates translation of hypoxia inducible factor-1 α (HIF-1 α), which ultimately increases production of proangiogenic factors such as VEGF-A and other molecules such as those involved in glucose transport. In well-oxygenated cells, HIF-1 α is degraded by the von Hippel-Lindau (VHL)

protein, which binds and targets it for destruction by the proteasome; loss of the VHL protein is a driving force in the development of some cancers, such as clear cell renal cancer^[47,48].

In hypoxic cells, such as those found in cancers, HIF-1 α translocates to the nucleus and combines with HIF-1 β , ultimately initiating the transcription of hypoxia-regulated genes, such as those for VEGF-A and inducible nitric oxide synthetase, which promote cell survival under anaerobic conditions, angiogenesis, metastasis^[49].

Overexpression of HIF-1 α has been associated with cancers of the breast, ovary, cervix, esophagus, brain, and head and neck higher aggressive and with a poorer prognosis; loss of HIF-1 activity decreases tumor growth, vascularization, and energy metabolism. mTOR inhibition can decrease HIF-1 α levels and inhibits VEGF production^[32-33,50].

Finally mTORC1 has a role also in regulating DNA damage caused by agents such as cisplatin. DNA damage activates p53. p53 triggers DNA repair, which allows the cell to survive, or, failing that, p53 initiates cell death. mTOR regulates production of p21, a cell cycle inhibitor that allows DNA repair. mTOR inhibition blocks p21 translation, forcing cell death even when the DNA damage is otherwise nonlethal. By this way mTOR inhibition can enhance the activity of certain drugs such as cisplatin and other platinum derivatives^[51].

Deregulation of mTOR pathways and risk of cancer

Deregulation of the mTOR-linked pathways increases the risk of developing cancer or have been identified in many cancers (Figure 4).

As a consequence the role of genetics in cancer development both in transplant patients and in general population is easy to be understood.

Growth factor receptors are altered in many cancers. Frequently, a deletion of the ligand-binding domain of EGF receptor (EGFR), a transmembrane protein with tyrosine kinase activity, causes constitutive activation of the receptor in the absence of ligand binding^[52].

Some of mTOR inhibitors as p53 and PTEN are often deleted or mutated in human cancer. Such kind of tumor cells are extremely sensible to the effect of mTOR inhibitors^[53,54].

In detail deregulation of the pathway can include overexpression of growth factors, overexpression or mutations of growth factor receptors, loss of tumor suppressor genes, and gain-of function mutations in mTOR-linked pathways, such as: (1) Inappropriate signaling through members of the human epidermal growth factor receptor (HER/EGFR) family in lung, colon, and breast cancers^[55-57]; (2) Activation of the estrogen receptor through ligand independent pathways linked to mTOR in breast cancer^[58]; (3) High levels of IGF-1 or expression of IGF-1 receptor in breast, prostate, lung, thyroid, and kidney cancers, melanoma, and sarcoma^[59-65]; (4) Increase Ras or PI3K signaling through activating mutations or loss-of-function mutations in tumor suppressor genes in

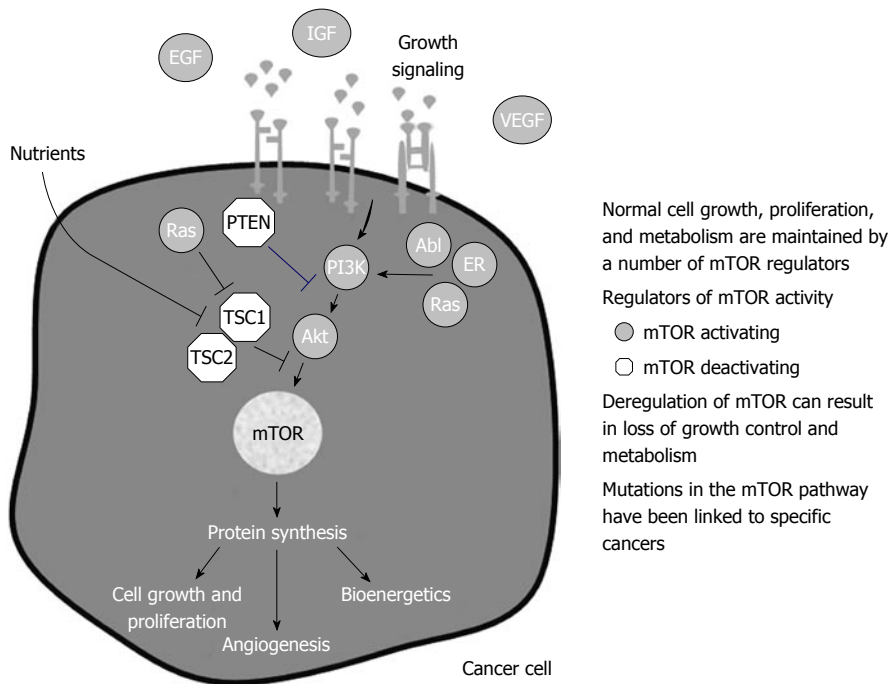


Figure 4 Mammalian target of rapamycin pathway is deregulated by mutations in cancer. PI3K: Phosphoinositide 3-kinase; mTOR: Mammalian target of rapamycin; IGF: Insulin like growth factor; EGF: Epidermal growth factor; VEGF: Vascular endothelial growth factor; ER: Estrogen receptor; TSC: Tuberous sclerosis complex.

Table 3 Mammalian target of rapamycin linked pathway deregulations in selected cancers

Lung	EGFR	32-60
	p-AKT	23-50
	Ras	30
	PTEN	24
	HER2	5
	PI3K	4
Kidney	TGF- α /TGF- β 1	60-100
	VHL	30-50
	IGF-1/IGF-1R	39-69
	p-AKT	38
	PTEN	31
	TSC1/TSC2	
Breast	p-Akt	42
	PTEN	15-41
	HER2	30-36
	PI3K	18-26
	EGFR	6
NET	TSC1/TSC2	
	IGF-1/IGF-1R	
	VHL	
Colon	Ras	50
	p-Akt	46
	PTEN	35
	PI3K	20-32
	EGFR	8
	HER2	3

EGFR: Epidermal growth factor receptor; HER: Human epidermal growth factor receptor; PI3K: Phosphoinositide 3-kinase; TGF: Transforming growth factor; VHL: von Hippel-Lindau; IGF: Insulin like growth factor; IGF-1R: IGF-1 receptor; TSC: Tuberous sclerosis complex.

pancreas, colon, thyroid, lung, leukemia, brain, gastric, breast, ovarian, prostate, endometrial, and oral squamous

cancers and melanoma^[66-75]; (5) Formation of the Bcr-Abl fusion gene, which causes Ph+ chronic myelogenous leukemia^[76]; and (6) Deregulated signaling or cross-talk through mTOR linked pathways can increase mTOR activity; mTOR inhibition could counteract this deregulated signaling. This represents the rationale because combining an agent that directly targets mTOR with an agent that targets a deregulation in an mTOR-linked pathway could produce more profound anticancer activity than either agent alone, particularly in cancers that have lost function of the tumor suppressor gene, PTEN^[77].

In the last decade a number of mTORC1 activating molecules have been found abnormally high (gain of function) and linked to specific cancers. PI3K is abnormally high in a variety of human cancers, as well as AKT^[78]. Rheb and ras have similarly been found abnormally high in human cancers^[79]. Also the effectors of mTOR have been found overexpressed in human cancers, in breast cancers and correlate with poor prognosis^[80]. Similarly, among tumor suppressors, mutations linked to tumor development have been found. Loss of PTEN is linked to hamartoma syndromes, as well as TSC and the serine threonine kinase 11 (LKB1)^[81]. P53 is mutated in the majority of human tumors. NF1 mutation is associated to neurofibromatosis type 1^[82].

In selected human cancer mTOR linked pathway deregulations has been found as shown in Table 3: Lung cancer: deregulation of EGFR, AKT, Ras, PTEN and PI3K in a range from 4% to 60%; Kidney cancer: deregulation of TGF, VHL, IGF-1/IGF-1R, AKT, PTEN TSC1/2 in a range from 31% to 100%; Breast cancer: deregulation of AKT, PTEN, PI3K, EGFR in a range from

6% to 42%; Neuroendocrine tumors: VHL, IGF-1/IGF-1R, TSC1/2; and colon carcinoma: EGFR, PI3K, PTEN, AKT, Ras in a range from 3% to 50%.

In summary aberrant signaling through upstream pathways can activate mTOR inappropriately: (1) Abnormal cell growth, proliferation, and angiogenesis; and (2) Survival of cancer cells in the nutrient- and oxygen-depleted tumor environment.

TARGETING mTOR PATHWAY IN CANCER: FROM TRANSPLANT PATIENTS TO GENERAL POPULATION

Targeting deregulated pathways

Targeting deregulated pathways has been a successful clinical strategy in cancer and a combination therapy targeting mTOR and deregulated pathways may provide enhanced anticancer activity^[56,58].

As already outlined and as a consequence of the aforementioned pathogenesis, a two hits therapy or a combination therapy targeting both upstream signaling and mTORC1 is a highly promising strategy^[31,77].

Overall four groups of agents have been developed for targeting solid cancers, alone or in combination: (1) Agents targeting EGFR; (2) Agents targeting IGF-1R; (3) Agents targeting VEGF/VEGFR; and (4) Agents targeting multi-kinase, among which the mTORIs have a prevalent role^[71,83].

Targeting deregulated pathways in cancer after transplantation

The beneficial effect of mTORIs on cancer prevention in transplant patients has been documented in the aforementioned clinical trials.

Recently a beneficial effect of rapamycin for Kaposi's sarcoma in renal-transplant recipients has been reported in 15 patients^[84].

In a different study a switch from CNIs to mTORIs has been performed in 53 renal transplant recipients developing non melanoma skin cancer after transplantation. A remission was observed in 37 patients with minimal adverse events reported^[85].

EVL has been used in liver transplant patients with *de novo* hepatocellular carcinoma after liver transplantation. The probability of survival in 10 patients of the EVL group was significantly greater than the observed in a historical cohort of 14 similar patients who did not receive EVL (HR = 4.6, $P = 0.008$)^[86].

Targeting deregulated pathways in cancers in general population

Thinking with the old concept that reduction in immune surveillance is the main factor in cancer genesis, could seem paradoxical the use of immunosuppressive agents like mTORIs in the treatment of cancer in patients not needing immunosuppressive therapy. It is not so if we look to the proven involvement of mTOR pathways in

cancer development. The block of abnormal mTOR pathways united with other antineoplastic agents seems now the best therapeutic approach.

Indeed mTORIs and EVL in particular have proven be effective in targeting cancer also in general population, independently from transplantation.

Many hematological malignancies have aberrant activation of the mTOR and related signaling pathways. Accordingly mTOR inhibitors, a class of signal transduction inhibitors, originally developed as immunosuppressive agents, are being investigated in preclinical models and clinical trials for a number of hematological malignancies^[50,87,88].

Several data indicate that pharmacological agents that target PI3K, AKT, or FRAP in prostate cancer cells, inhibit HIF-1 α expression and that such inhibition may contribute to therapeutic efficacy^[89,90].

Recently FDA approved EVL in metastatic renal cell carcinoma after a trial documenting in 272 patients affected by such carcinoma the efficacy of EVL with respect to standard therapy^[91].

In a recent study (RADIANT-3) 410 patients with low grade or intermediate grade pancreatic neuroendocrine tumors were randomized to receive EVL or placebo. EVL significantly prolonged progression-free survival and was associated with a low rate of severe adverse events^[92].

In the BOLERO-2 trial mTOR inhibitor EVL, added to endocrine therapy showed antitumor activity. In such patients indeed the resistance to endocrine therapy in breast cancer is associated with activation of the mTOR intracellular signaling pathway^[93].

Recently a synergistic effect of mTOR inhibitor and chemotherapy in a rat model of hepatocellular carcinoma has been found^[94]. Many clinical trials now at their final or preliminary publication, are planned or are actively recruiting patients for treatment of liver carcinoma with mTOR inhibitors.

CONCLUSION

mTOR inhibitors are a group of parent drugs with a well defined immunosuppressive property and are widely used as immunosuppressant drugs in kidney, liver, lung and heart transplantation. Thanks to their mechanism of action, favouring apoptosis and inhibiting proliferation of both immune and non immune cells, such drugs have a documented antineoplastic action in transplant patients. Some of them as SRL (rapamycin), EVL (afnitor/certican), temSRL (torisel) and deforolimus are either launched or in advanced development stage in cancer therapy also outside transplantation.

As aforementioned their mechanism of action is still now not fully understood and most probably this group of drugs will prove to be effective in controlling some types of cancer, and other not. The complexity of the mTOR pathway, mainly considering the negative feedback loops that exist, suggests that only properly designed

clinical trials will provide the final answer. Nonetheless, our present knowledge of the mTOR pathway supports such trials.

REFERENCES

- Kasiske BL, Snyder JJ, Gilbertson DT, Wang C. Cancer after kidney transplantation in the United States. *Am J Transplant* 2004; **4**: 905-913
- Buell JF, Gross TG, Woodle ES. Malignancy after transplantation. *Transplantation* 2005; **80**: S254-S264
- Morath C, Mueller M, Goldschmidt H, Schwenger V, Opelz G, Zeier M. Malignancy in renal transplantation. *J Am Soc Nephrol* 2004; **15**: 1582-1588
- Kauffman HM, Cherikh WS, McBride MA, Cheng Y, Hanto DW. Post-transplant de novo malignancies in renal transplant recipients: the past and present. *Transpl Int* 2006; **19**: 607-620
- Dantal J, Hourmant M, Cantarovich D, Giral M, Blanche G, Dreno B, Souillou JP. Effect of long-term immunosuppression in kidney-graft recipients on cancer incidence: randomised comparison of two cyclosporin regimens. *Lancet* 1998; **351**: 623-628
- Guba M, Graeb C, Jauch KW, Geissler EK. Pro- and anti-cancer effects of immunosuppressive agents used in organ transplantation. *Transplantation* 2004; **77**: 1777-1782
- Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell* 2000; **100**: 57-70
- Geissler EK, Schlitt HJ. The relation between immunosuppressive agents and malignancy. *Curr Opin Organ Transplant* 2004; **9**: 394-399
- Gaumann A, Schlitt HJ, Geissler EK. Immunosuppression and tumor development in organ transplant recipients: the emerging dualistic role of rapamycin. *Transpl Int* 2008; **21**: 207-217
- Hojo M, Morimoto T, Maluccio M, Asano T, Morimoto K, Lagman M, Shimbo T, Suthanthiran M. Cyclosporine induces cancer progression by a cell-autonomous mechanism. *Nature* 1999; **397**: 530-534
- Guba M, von Breitenbuch P, Steinbauer M, Koehl G, Flegel S, Hornung M, Bruns CJ, Zuelke C, Farkas S, Anthuber M, Jauch KW, Geissler EK. Rapamycin inhibits primary and metastatic tumor growth by antiangiogenesis: involvement of vascular endothelial growth factor. *Nat Med* 2002; **8**: 128-135
- Basu A, Contreras AG, Datta D, Flynn E, Zeng L, Cohen HT, Briscoe DM, Pal S. Overexpression of vascular endothelial growth factor and the development of post-transplantation cancer. *Cancer Res* 2008; **68**: 5689-5698
- Viganò M, Tuzcu M, Benza R, Boissonnat P, Haverich A, Hill J, Laufer G, Love R, Parameshwar J, Pulpón LA, Renlund D, Abeywickrama K, Cretin N, Starling RC, Eisen HJ. Prevention of acute rejection and allograft vasculopathy by everolimus in cardiac transplants recipients: a 24-month analysis. *J Heart Lung Transplant* 2007; **26**: 584-592
- Zimmerman MA, Trotter JF, Wachs M, Bak T, Campsen J, Skibba A, Kam I. Sirolimus-based immunosuppression following liver transplantation for hepatocellular carcinoma. *Liver Transpl* 2008; **14**: 633-638
- Gabardi S, Baroletti SA. Everolimus: a proliferation signal inhibitor with clinical applications in organ transplantation, oncology, and cardiology. *Pharmacotherapy* 2010; **30**: 1044-1056
- Huang S, Bjornsti MA, Houghton PJ. Rapamycins: mechanism of action and cellular resistance. *Cancer Biol Ther* 2003; **2**: 222-232
- Biecker E, De Gottardi A, Neef M, Unternährer M, Schneider V, Ledermann M, Sägeser H, Shaw S, Reichen J. Long-term treatment of bile duct-ligated rats with rapamycin (sirolimus) significantly attenuates liver fibrosis: analysis of the underlying mechanisms. *J Pharmacol Exp Ther* 2005; **313**: 952-961
- McKenna GJ, Trotter JF, Klintmalm E, Onaca N, Ruiz R, Jennings LW, Neri M, O'Leary JG, Davis GL, Levy MF, Goldstein RM, Klintmalm GB. Limiting hepatitis C virus progression in liver transplant recipients using sirolimus-based immunosuppression. *Am J Transplant* 2011; **11**: 2379-2387
- Luan FL, Hojo M, Maluccio M, Yamaji K, Suthanthiran M. Rapamycin blocks tumor progression: unlinking immunosuppression from antitumor efficacy. *Transplantation* 2002; **73**: 1565-1572
- Nourse J, Firpo E, Flanagan WM, Coats S, Polyak K, Lee MH, Massague J, Crabtree GR, Roberts JM. Interleukin-2-mediated elimination of the p27Kip1 cyclin-dependent kinase inhibitor prevented by rapamycin. *Nature* 1994; **372**: 570-573
- Nepomuceno RR, Balatoni CE, Natkunam Y, Snow AL, Krams SM, Martinez OM. Rapamycin inhibits the interleukin 10 signal transduction pathway and the growth of Epstein Barr virus B-cell lymphomas. *Cancer Res* 2003; **63**: 4472-4480
- Mathew T, Kreis H, Friend P. Two-year incidence of malignancy in sirolimus-treated renal transplant recipients: results from five multicenter studies. *Clin Transplant* 2004; **18**: 446-449
- Campistol JM, Eris J, Oberbauer R, Friend P, Hutchison B, Morales JM, Claesson K, Stallone G, Russ G, Rostaing L, Kreis H, Burke JT, Braut Y, Scarola JA, Neylan JF. Sirolimus therapy after early cyclosporine withdrawal reduces the risk for cancer in adult renal transplantation. *J Am Soc Nephrol* 2006; **17**: 581-589
- Schena FP, Pascoe MD, Alberu J, del Carmen Rial M, Oberbauer R, Brennan DC, Campistol JM, Racusen L, Polinsky MS, Goldberg-Alberts R, Li H, Scarola J, Neylan JF. Conversion from calcineurin inhibitors to sirolimus maintenance therapy in renal allograft recipients: 24-month efficacy and safety results from the CONVERT trial. *Transplantation* 2009; **87**: 233-242
- Webster AC, Lee VW, Chapman JR, Craig JC. Target of rapamycin inhibitors (sirolimus and everolimus) for primary immunosuppression of kidney transplant recipients: a systematic review and meta-analysis of randomized trials. *Transplantation* 2006; **81**: 1234-1248
- Kauffman HM, Cherikh WS, Cheng Y, Hanto DW, Kahan BD. Maintenance immunosuppression with target-of-rapamycin inhibitors is associated with a reduced incidence of de novo malignancies. *Transplantation* 2005; **80**: 883-889
- Giamas G, Man YL, Hirner H, Bischof J, Kramer K, Khan K, Ahmed SS, Stebbing J, Knippschild U. Kinases as targets in the treatment of solid tumors. *Cell Signal* 2010; **22**: 984-1002
- Humar R, Kiefer FN, Berns H, Resink TJ, Battegay EJ. Hypoxia enhances vascular cell proliferation and angiogenesis in vitro via rapamycin (mTOR)-dependent signaling. *FASEB J* 2002; **16**: 771-780
- Edinger AL, Thompson CB. Akt maintains cell size and survival by increasing mTOR-dependent nutrient uptake. *Mol Biol Cell* 2002; **13**: 2276-2288
- Jaeschke A, Dennis PB, Thomas G. mTOR: a mediator of intracellular homeostasis. *Curr Top Microbiol Immunol* 2004; **279**: 283-298
- Mitsudomi T, Yatabe Y. Epidermal growth factor receptor in relation to tumor development: EGFR gene and cancer. *FEBS J* 2010; **277**: 301-308
- Shaw RJ, Cantley LC. Ras, PI(3)K and mTOR signalling controls tumour cell growth. *Nature* 2006; **441**: 424-430
- Wang X, Proud CG. The mTOR pathway in the control of protein synthesis. *Physiology (Bethesda)* 2006; **21**: 362-369
- Sarbassov DD, Ali SM, Sabatini DM. Growing roles for the mTOR pathway. *Curr Opin Cell Biol* 2005; **17**: 596-603
- Herman MA, Kahn BB. Glucose transport and sensing in the maintenance of glucose homeostasis and metabolic har-

- mony. *J Clin Invest* 2006; **116**: 1767-1775
- 36 **Motoshima H**, Goldstein BJ, Igata M, Araki E. AMPK and cell proliferation--AMPK as a therapeutic target for atherosclerosis and cancer. *J Physiol* 2006; **574**: 63-71
- 37 **Guertin DA**, Sabatini DM. Defining the role of mTOR in cancer. *Cancer Cell* 2007; **12**: 9-22
- 38 **Abraham RT**, Eng CH. Mammalian target of rapamycin as a therapeutic target in oncology. *Expert Opin Ther Targets* 2008; **12**: 209-222
- 39 **Plas DR**, Thompson CB. Akt-dependent transformation: there is more to growth than just surviving. *Oncogene* 2005; **24**: 7435-744
- 40 **Geissler EK**, Schlitt HJ, Thomas G. mTOR, cancer and transplantation. *Am J Transplant* 2008; **8**: 2212-2218
- 41 **Manning BD**, Cantley LC. Rheb fills a GAP between TSC and TOR. *Trends Biochem Sci* 2003; **28**: 573-576
- 42 **Lee DF**, Kuo HP, Chen CT, Hsu JM, Chou CK, Wei Y, Sun HL, Li LY, Ping B, Huang WC, He X, Hung JY, Lai CC, Ding Q, Su JL, Yang JY, Sahin AA, Hortobagyi GN, Tsai FJ, Tsai CH, Hung MC. IKK beta suppression of TSC1 links inflammation and tumor angiogenesis via the mTOR pathway. *Cell* 2007; **130**: 440-455
- 43 **Averous J**, Proud CG. When translation meets transformation: the mTOR story. *Oncogene* 2006; **25**: 6423-6435
- 44 **Mamane Y**, Petroulakis E, LeBacquer O, Sonenberg N. mTOR, translation initiation and cancer. *Oncogene* 2006; **25**: 6416-6422
- 45 **Ellisen LW**. Growth control under stress: mTOR regulation through the REDD1-TSC pathway. *Cell Cycle* 2005; **4**: 1500-1502
- 46 **Kaper F**, Dornhoefer N, Giaccia AJ. Mutations in the PI3K/PTEN/TSC2 pathway contribute to mammalian target of rapamycin activity and increased translation under hypoxic conditions. *Cancer Res* 2006; **66**: 1561-1569
- 47 **Powis G**, Kirkpatrick L. Hypoxia inducible factor-1alpha as a cancer drug target. *Mol Cancer Ther* 2004; **3**: 647-654
- 48 **Vaupel P**. The role of hypoxia-induced factors in tumor progression. *Oncologist* 2004; **9** Suppl 5: 10-17
- 49 **Stoeltzing O**, McCarty MF, Wey JS, Fan F, Liu W, Belcheva A, Bucana CD, Semenza GL, Ellis LM. Role of hypoxia-inducible factor 1alpha in gastric cancer cell growth, angiogenesis, and vessel maturation. *J Natl Cancer Inst* 2004; **96**: 946-956
- 50 **Haase VH**. Hypoxia-inducible factors in the kidney. *Am J Physiol Renal Physiol* 2006; **291**: F271-F281
- 51 **Beuvink I**, Boulay A, Fumagalli S, Zilbermann F, Ruetz S, O'Reilly T, Natt F, Hall J, Lane HA, Thomas G. The mTOR inhibitor RAD001 sensitizes tumor cells to DNA-damaged induced apoptosis through inhibition of p21 translation. *Cell* 2005; **120**: 747-759
- 52 **Croce CM**. Oncogenes and cancer. *N Engl J Med* 2008; **358**: 502-511
- 53 **Sansal I**, Sellers WR. The biology and clinical relevance of the PTEN tumor suppressor pathway. *J Clin Oncol* 2004; **22**: 2954-2963
- 54 **Neshat MS**, Mellinghoff IK, Tran C, Stiles B, Thomas G, Petersen R, Frost P, Gibbons JJ, Wu H, Sawyers CL. Enhanced sensitivity of PTEN-deficient tumors to inhibition of FRAP/mTOR. *Proc Natl Acad Sci USA* 2001; **98**: 10314-10319
- 55 **Cappuzzo F**, Hirsch FR, Rossi E, Bartolini S, Ceresoli GL, Bemis L, Haney J, Witta S, Danenberg K, Domenichini I, Ludovini V, Magrini E, Gregorc V, Doglioni C, Sidoni A, Tonato M, Franklin WA, Crino L, Bunn PA, Varella-Garcia M. Epidermal growth factor receptor gene and protein and gefitinib sensitivity in non-small-cell lung cancer. *J Natl Cancer Inst* 2005; **97**: 643-655
- 56 **Cunningham D**, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, Bets D, Mueser M, Harstick A, Verslype C, Chau I, Van Cutsem E. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004; **351**: 337-345
- 57 **Slamon DJ**, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, Fleming T, Eiermann W, Wolter J, Pegram M, Baselga J, Norton L. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001; **344**: 783-792
- 58 **Ali S**, Coombes RC. Endocrine-responsive breast cancer and strategies for combating resistance. *Nat Rev Cancer* 2002; **2**: 101-112
- 59 **Hankinson SE**, Willett WC, Colditz GA, Hunter DJ, Michaud DS, Deroo B, Rosner B, Speizer FE, Pollak M. Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. *Lancet* 1998; **351**: 1393-1396
- 60 **Chan JM**, Stampfer MJ, Giovannucci E, Gann PH, Ma J, Wilkinson P, Hennekens CH, Pollak M. Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. *Science* 1998; **279**: 563-566
- 61 **Minuto F**, Del Monte P, Barreca A, Fortini P, Cariola G, Ca-trambone G, Giordano G. Evidence for an increased somatomedin-C/insulin-like growth factor I content in primary human lung tumors. *Cancer Res* 1986; **46**: 985-988
- 62 **Belfiore A**, Pandini G, Vella V, Squatrito S, Vigneri R. Insulin/IGF-I hybrid receptors play a major role in IGF-I signaling in thyroid cancer. *Biochimie* 1999; **81**: 403-407
- 63 **Schips L**, Zigeuner R, Ratschek M, Rehak P, Rüschoff J, Langner C. Analysis of insulin-like growth factors and insulin-like growth factor I receptor expression in renal cell carcinoma. *Am J Clin Pathol* 2004; **122**: 931-937
- 64 **All-Ericsson C**, Girnita L, Seregard S, Bartolazzi A, Jager MJ, Larsson O. Insulin-like growth factor-1 receptor in uveal melanoma: a predictor for metastatic disease and a potential therapeutic target. *Invest Ophthalmol Vis Sci* 2002; **43**: 1-8
- 65 **Burrow S**, Andrulis IL, Pollak M, Bell RS. Expression of insulin-like growth factor receptor, IGF-1, and IGF-2 in primary and metastatic osteosarcoma. *J Surg Oncol* 1998; **69**: 21-27
- 66 **Bos JL**. ras oncogenes in human cancer: a review. *Cancer Res* 1989; **49**: 4682-4689
- 67 **Samuels Y**, Wang Z, Bardelli A, Silliman N, Ptak J, Szabo S, Yan H, Gazdar A, Powell SM, Riggins GJ, Willson JK, Markowitz S, Kinzler KW, Vogelstein B, Velculescu VE. High frequency of mutations of the PIK3CA gene in human cancers. *Science* 2004; **304**: 554
- 68 **Levine DA**, Bogomolny F, Yee CJ, Lash A, Barakat RR, Borgen PI, Boyd J. Frequent mutation of the PIK3CA gene in ovarian and breast cancers. *Clin Cancer Res* 2005; **11**: 2875-2878
- 69 **Itoh N**, Semba S, Ito M, Takeda H, Kawata S, Yamakawa M. Phosphorylation of Akt/PKB is required for suppression of cancer cell apoptosis and tumor progression in human colorectal carcinoma. *Cancer* 2002; **94**: 3127-3134
- 70 **Zhou X**, Tan M, Stone Hawthorne V, Klos KS, Lan KH, Yang Y, Yang W, Smith TL, Shi D, Yu D. Activation of the Akt/mammalian target of rapamycin/4E-BP1 pathway by ErbB2 overexpression predicts tumor progression in breast cancers. *Clin Cancer Res* 2004; **10**: 6779-6788
- 71 **Mandal M**, Kim S, Younes MN, Jasser SA, El-Naggar AK, Mills GB, Myers JN. The Akt inhibitor KP372-1 suppresses Akt activity and cell proliferation and induces apoptosis in thyroid cancer cells. *Br J Cancer* 2005; **92**: 1899-1905
- 72 **David O**, Jett J, LeBeau H, Dy G, Hughes J, Friedman M, Brody AR. Phospho-Akt overexpression in non-small cell lung cancer confers significant stage-independent survival disadvantage. *Clin Cancer Res* 2004; **10**: 6865-6871
- 73 **Dai DL**, Martinka M, Li G. Prognostic significance of activated Akt expression in melanoma: a clinicopathologic study of 292 cases. *J Clin Oncol* 2005; **23**: 1473-1482
- 74 **Lim J**, Kim JH, Paeng JY, Kim MJ, Hong SD, Lee JI, Hong SP. Prognostic value of activated Akt expression in oral squamous cell carcinoma. *J Clin Pathol* 2005; **58**: 1199-1205
- 75 **Soria JC**, Lee HY, Lee JI, Wang L, Issa JP, Kemp BL, Liu DD,

- Kurie JM, Mao L, Khuri FR. Lack of PTEN expression in non-small cell lung cancer could be related to promoter methylation. *Clin Cancer Res* 2002; **8**: 1178-1184
- 76 **Kantarjian H**, Sawyers C, Hochhaus A, Guilhot F, Schiffer C, Gambacorti-Passerini C, Niederwieser D, Resta D, Capdeville R, Zoellner U, Talpaz M, Druker B, Goldman J, O'Brien SG, Russell N, Fischer T, Ottmann O, Cony-Makhoul P, Facon T, Stone R, Miller C, Tallman M, Brown R, Schuster M, Loughran T, Gratwohl A, Mandelli F, Saglio G, Lazzarino M, Russo D, Baccarani M, Morra E. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. *N Engl J Med* 2002; **346**: 645-652
- 77 **Hynes NE**, Lane HA. ERBB receptors and cancer: the complexity of targeted inhibitors. *Nat Rev Cancer* 2005; **5**: 341-354
- 78 **Vivanco I**, Sawyers CL. The phosphatidylinositol 3-Kinase AKT pathway in human cancer. *Nat Rev Cancer* 2002; **2**: 489-501
- 79 **Coleman ML**, Marshall CJ, Olson MF. RAS and RHO GTPases in G1-phase cell-cycle regulation. *Nat Rev Mol Cell Biol* 2004; **5**: 355-366
- 80 **Bjornsti MA**, Houghton PJ. The TOR pathway: a target for cancer therapy. *Nat Rev Cancer* 2004; **4**: 335-348
- 81 **Inoki K**, Ouyang H, Li Y, Guan KL. Signaling by target of rapamycin proteins in cell growth control. *Microbiol Mol Biol Rev* 2005; **69**: 79-100
- 82 **Wullschlegel S**, Loewith R, Hall MN. TOR signaling in growth and metabolism. *Cell* 2006; **124**: 471-484
- 83 **Höpfner M**, Schuppan D, Scherübl H. Growth factor receptors and related signalling pathways as targets for novel treatment strategies of hepatocellular cancer. *World J Gastroenterol* 2008; **14**: 1-14
- 84 **Stallone G**, Schena A, Infante B, Di Paolo S, Loverre A, Maggio G, Ranieri E, Gesualdo L, Schena FP, Grandaliano G. Sirolimus for Kaposi's sarcoma in renal-transplant recipients. *N Engl J Med* 2005; **352**: 1317-1323
- 85 **de Fijter JW**. Use of proliferation signal inhibitors in non-melanoma skin cancer following renal transplantation. *Nephrol Dial Transplant* 2007; **22** Suppl 1: i23-i26
- 86 **Gomez-Camarero J**, Salcedo M, Rincon D, Lo Iacono O, Ripoll C, Hernando A, Sanz C, Clemente G, Bañares R. Use of everolimus as a rescue immunosuppressive therapy in liver transplant patients with neoplasms. *Transplantation* 2007; **84**: 786-791
- 87 **Shi Y**, Gera J, Hu L, Hsu JH, Bookstein R, Li W, Lichtenstein A. Enhanced sensitivity of multiple myeloma cells containing PTEN mutations to CCI-779. *Cancer Res* 2002; **62**: 5027-5034
- 88 **Teachey DT**, Grupp SA, Brown VI. Mammalian target of rapamycin inhibitors and their potential role in therapy in leukaemia and other haematological malignancies. *Br J Haematol* 2009; **145**: 569-580
- 89 **Majumder PK**, Febbo PG, Bikoff R, Berger R, Xue Q, McMahon LM, Manola J, Brugarolas J, McDonnell TJ, Golub TR, Loda M, Lane HA, Sellers WR. mTOR inhibition reverses Akt-dependent prostate intraepithelial neoplasia through regulation of apoptotic and HIF-1-dependent pathways. *Nat Med* 2004; **10**: 594-601
- 90 **Zhong H**, Chiles K, Feldser D, Laughner E, Hanrahan C, Georgescu MM, Simons JW, Semenza GL. Modulation of hypoxia-inducible factor 1alpha expression by the epidermal growth factor/phosphatidylinositol 3-kinase/PTEN/AKT/FRAP pathway in human prostate cancer cells: implications for tumor angiogenesis and therapeutics. *Cancer Res* 2000; **60**: 1541-1545
- 91 **Motzer RJ**, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, Grünwald V, Thompson JA, Figlin RA, Hollaender N, Urbanowitz G, Berg WJ, Kay A, Lebwohl D, Ravaud A. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet* 2008; **372**: 449-456
- 92 **Yao JC**, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, Hobday TJ, Okusaka T, Capdevila J, de Vries EG, Tomassetti P, Pavel ME, Hoosen S, Haas T, Lincy J, Lebwohl D, Öberg K. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med* 2011; **364**: 514-523
- 93 **Baselga J**, Campone M, Piccart M, Burris HA, Rugo HS, Sahmoud T, Noguchi S, Gnant M, Pritchard KI, Lebrun F, Beck JT, Ito Y, Yardley D, Deleu I, Perez A, Bachelot T, Vittori L, Xu Z, Mukhopadhyay P, Lebwohl D, Hortobagyi GN. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med* 2012; **366**: 520-529
- 94 **Treiber G**. mTOR inhibitors for hepatocellular cancer: a forward-moving target. *Expert Rev Anticancer Ther* 2009; **9**: 247-261

S- Editor Wang JL L- Editor A E- Editor Zheng XM

Acknowledgments to reviewers of *World Journal of Transplantation*

We acknowledge our sincere thanks to our reviewers. Many reviewers have contributed their expertise and time to the peer review, a critical process to ensure the quality of our World Series Journals. Both the editors of the journals and authors of the manuscripts submitted to the journals are grateful to the following reviewers for reviewing the articles (either published or rejected) over the past period of time.

Andrea De Gottardi, MD, PhD, Assistant Professor, Clinic of Visceral Surgery and Medicine, Hepatology, Freiburgstrasse, CH-3010 Berne, Inselspital, Switzerland

Yu-Fan Cheng, MD, Department of Radiology, Chang Gung Memorial Hospital Kaohsiung Medical Center, 123, TA Pei Road, Niao Sung Hsiang, Kaohsiung Hsien 833, Taiwan, China

Sarah Anne Hosgood, Miss, BSc, Department of Infection, Immunity and Inflammation, Transplant Group, Leicester General Hospital, University of Leicester, LE5 4PW, United Kingdom

Ahad Eshraghian, MD, Department of Internal medicine, Namazi hospital, Shiraz University of medical science, Shiraz, 71345-1377, Iran

Frank JMF Dor, MD, PhD, Division of Transplant Surgery, Department of Surgery, Erasmus MC Rotterdam, room H-811, PO BOX 2040, 3000 CA Rotterdam, The Netherlands

Olivier Detry, MD, PhD, Associate Professor, Department of

Abdominal Surgery and Transplantation, University of Liège, CHU Liège, Sart Tilman B35, B4000 Liège, Wallonia, Belgium

Andres Beiras-Fernandez, MD, PhD, Department of Cardiac Surgery, University Hospital Munich, Marchioninistraße 15, 81377 Munich, Germany

Ilka FSF Boin, MD, PhD, Associate Professor, Director of Unit of Liver Transplantation, HC, Unicamp, Surgery Department, Faculty of Medical Sciences, State University of Campinas, Av. Carlos Chagas, 420, Postal Code 13983-000, Campinas, SP, Brazil

Costas Fourtounas, MD, PhD, Associate Professor, Department of Nephrology, Patras University Hospital, Rio-Patras 26500, Greece

Wenda Gao, PhD, Assistant Professor, Department of Medicine, Transplant Institute, Beth Israel Deaconess Med Ctr, SL-427, Harvard Medical School, Boston, MA 02215, United States

Mehdi Hamadani, MD, Assistant Professor of Medicine, Hematology, Oncology, West Virginia University, PO Box 9162, 1 Medical Center Drive, Morgantown, WV 26506, United States

Kuzhuvelil B Harikumar, Post Doctoral Associate, Department of Biochemistry, Virginia Commonwealth University, 1101 East Marshall St, Richmond VA 23298, United States

Walid Mohamed El Moghazy, MD, PhD, Department of Hepatobiliary, Pancreas and Transplant Surgery, Kyoto University Hospital, 54 Kawara-cho, Shogoin, Sakyo-ku, Kyoto city, Kyoto, 606-8507, Japan



Events Calendar 2012

January 29 - 31, 2012

2nd Joint AIDPIT and EPITA

Winter Symposium & 31st AIDPIT

Workshop

Innsbruck, Austria

February 1 - 5, 2012

2012 BMT Tandem Meetings

American Society for Blood and

Marrow Transplantation

Manchester Grand Hyatt,

San Diego, CA, United States

February 22 - 24, 2012

British Transplantation Society 15th

Annual Congress

Glasgow, Scotland

February 23 - 25, 2012

2012 Canadian Society of

Transplantation Annual Scientific

Conference

Fairmont Château Frontenac,

Québec, Canada

March 8 - 10, 2012

3rd International Conference on

Transplantomics and Biomarkers in

Organ Transplantation

La Jolla/San Diego,

CA, United States

April 18 - 21, 2012

The International Society for Heart

and Lung Transplantation (ISHLT),

32nd Annual Meeting and Scientific

Sessions

Prague, Czech Republic

April 25 - 27, 2012

United Network for Organ

Sharing's 20th Annual Transplant

Management Forum

Wyndham Rio Mar Beach Resort,

Puerto Rico

June 2 - 6, 2012

2012 American Transplant Congress

John B. Hynes Convention Center,

Boston, MA, United States

July 15 - 19, 2011

24th International Congress of the

Transplantation Society

Berlin, Germany

September 13 - 15, 2012

ELITA - LICAGE LIVER MEETING

and 4th ELITA Split-Liver Course

Ghent, Belgium

September 29 - 30, 2012

Advances in nephrology, dialysis,

Kidney Transplantation

Odessa, Ukraine

October 5 - 7, 2012

V Congress of Transplantologists

Kharkiv, Ukraine

October 5 - 7, 2012

2012 European Organ Donation

Congress, 24th ETCO-EDC

Dubrovnik, Croatia

October 12 - 14, 2012

ESOT and AST Joint Meeting -

Transformational therapies and

diagnostics in transplantation

Nice, France

November 2 - 4, 2012

5th ELPAT Invitational Working

Groups Meeting

Sicily, Italy

GENERAL INFORMATION

World Journal of Transplantation (*World J Transplant*, *WJT*, online ISSN 2220-3230, DOI: 10.5500) is a bimonthly peer-reviewed, online, open-access (OA), journal supported by an editorial board consisting of 100 experts in transplantation from 29 countries.

The biggest advantage of the OA model is that it provides free, full-text articles in PDF and other formats for experts and the public without registration, which eliminates the obstacle that traditional journals possess and usually delays the speed of the propagation and communication of scientific research results. The open access model has been proven to be a true approach that may achieve the ultimate goal of the journals, i.e. the maximization of the value to the readers, authors and society.

Maximization of personal benefits

The role of academic journals is to exhibit the scientific levels of a country, a university, a center, a department, and even a scientist, and build an important bridge for communication between scientists and the public. As we all know, the significance of the publication of scientific articles lies not only in disseminating and communicating innovative scientific achievements and academic views, as well as promoting the application of scientific achievements, but also in formally recognizing the "priority" and "copyright" of innovative achievements published, as well as evaluating research performance and academic levels. So, to realize these desired attributes of *WJT* and create a well-recognized journal, the following four types of personal benefits should be maximized. The maximization of personal benefits refers to the pursuit of the maximum personal benefits in a well-considered optimal manner without violation of the laws, ethical rules and the benefits of others. (1) Maximization of the benefits of editorial board members: The primary task of editorial board members is to give a peer review of an unpublished scientific article via online office system to evaluate its innovativeness, scientific and practical values and determine whether it should be published or not. During peer review, editorial board members can also obtain cutting-edge information in that field at first hand. As leaders in their field, they have priority to be invited to write articles and publish commentary articles. We will put peer reviewers' names and affiliations along with the article they reviewed in the journal to acknowledge their contribution; (2) Maximization of the benefits of authors: Since *WJT* is an OA journal, readers around the world can immediately download and read, free of charge, high-quality, peer-reviewed articles from *WJT* official website, thereby realizing the goals and significance of the communication between authors and peers as well as public reading; (3) Maximization of the benefits of readers: Readers can read or use, free of charge, high-quality peer-reviewed articles without any limits, and cite the arguments, viewpoints, concepts, theories, methods, results, conclusion or facts and data of pertinent literature so as to validate the innovativeness, scientific and practical values of their own research achievements, thus ensuring that their articles have novel arguments or viewpoints, solid evidence and correct conclusion; and (4) Maximization of the benefits of employees: It is an iron law that a first-class journal is unable to exist without first-class editors, and only first-class editors can create a first-class academic journal. We insist on strengthening our team cultivation and construction so that every employee, in an open, fair and transparent environment, could contribute their wisdom to edit and publish high-quality articles, thereby realizing the

maximization of the personal benefits of editorial board members, authors and readers, and yielding the greatest social and economic benefits.

Aims and scope

WJT aims to report rapidly new theories, methods and techniques for prevention, diagnosis, treatment, rehabilitation and nursing in the field of transplantation. *WJT* covers topics concerning organ and tissue donation and preservation; tissue injury, repair, inflammation, and aging; immune recognition, regulation, effector mechanisms, and opportunities for induction of tolerance, thoracic transplantation (heart, lung), abdominal transplantation (kidney, liver, pancreas, islets), transplantation of tissues, cell therapy and islet transplantation, clinical transplantation, experimental transplantation, immunobiology and genomics, xenotransplantation, and transplantation-related traditional medicine, and integrated Chinese and Western medicine. The journal also publishes original articles and reviews that report the results of transplantation-related applied and basic research in fields such as immunology, physiopathology, cell biology, pharmacology, medical genetics, and pharmacology of Chinese herbs.

Columns

The columns in the issues of *WJT* will include: (1) Editorial: To introduce and comment on the substantial advance and its importance in the fast-developing areas; (2) Frontier: To review the most representative achievements and comment on the current research status in the important fields, and propose directions for the future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (6) Review: To systemically review the most representative progress and unsolved problems in the major scientific disciplines, comment on the current research status, and make suggestions on the future work; (7) Original Articles: To originally report the innovative and valuable findings in transplantation; (8) Brief Articles: To briefly report the novel and innovative findings in transplantation; (9) Case Report: To report a rare or typical case; (10) Letters to the Editor: To discuss and make reply to the contributions published in *WJT*, or to introduce and comment on a controversial issue of general interest; (11) Book Reviews: To introduce and comment on quality monographs of transplantation; and (12) Guidelines: To introduce consensus and guidelines reached by international and national academic authorities worldwide on the research in transplantation.

Name of journal

World Journal of Transplantation

ISSN

ISSN 2220-3230 (online)

Editor-in-Chief

Maurizio Salvadori, MD, Professor, Renal Unit, Careggi University Hospital, Viale Pieraccini 18, Florence 50139, Italy

Instructions to authors

Editorial Office

World Journal of Transplantation

Editorial Department: Room 903, Building D,

Ocean International Center,

No. 62 Dongsihuan Zhonglu,

Chaoyang District, Beijing 100025, China

E-mail: wjt@wjgnet.com

<http://www.wjgnet.com>

Telephone: +86-10-85381891

Fax: +86-10-85381893

Indexed and Abstracted in

Digital Object Identifier.

Published by

Baishideng Publishing Group Co., Limited

SPECIAL STATEMENT

All articles published in this journal represent the viewpoints of the authors except where indicated otherwise.

Biostatistical editing

Statistical review is performed after peer review. We invite an expert in Biomedical Statistics to evaluate the statistical method used in the paper, including *t*-test (group or paired comparisons), chi-squared test, Redit, probit, logit, regression (linear, curvilinear, or stepwise), correlation, analysis of variance, analysis of covariance, *etc.* The reviewing points include: (1) Statistical methods should be described when they are used to verify the results; (2) Whether the statistical techniques are suitable or correct; (3) Only homogeneous data can be averaged. Standard deviations are preferred to standard errors. Give the number of observations and subjects (*n*). Losses in observations, such as drop-outs from the study should be reported; (4) Values such as ED50, LD50, IC50 should have their 95% confidence limits calculated and compared by weighted probit analysis (Bliss and Finney); and (5) The word 'significantly' should be replaced by its synonyms (if it indicates extent) or the *P* value (if it indicates statistical significance).

Conflict-of-interest statement

In the interests of transparency and to help reviewers assess any potential bias, *WJT* requires authors of all papers to declare any competing commercial, personal, political, intellectual, or religious interests in relation to the submitted work. Referees are also asked to indicate any potential conflict they might have reviewing a particular paper. Before submitting, authors are suggested to read "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Ethical Considerations in the Conduct and Reporting of Research: Conflicts of Interest" from International Committee of Medical Journal Editors (ICMJE), which is available at: http://www.icmje.org/ethical_4conflicts.html.

Sample wording: [Name of individual] has received fees for serving as a speaker, a consultant and an advisory board member for [names of organizations], and has received research funding from [names of organization]. [Name of individual] is an employee of [name of organization]. [Name of individual] owns stocks and shares in [name of organization]. [Name of individual] owns patent [patent identification and brief description].

Statement of informed consent

Manuscripts should contain a statement to the effect that all human studies have been reviewed by the appropriate ethics committee or it should be stated clearly in the text that all persons gave their informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study should be omitted. Authors should also draw attention to the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964, as revised in 2004).

Statement of human and animal rights

When reporting the results from experiments, authors should follow the highest standards and the trial should conform to Good Clinical

Practice (for example, US Food and Drug Administration Good Clinical Practice in FDA-Regulated Clinical Trials; UK Medicines Research Council Guidelines for Good Clinical Practice in Clinical Trials) and/or the World Medical Association Declaration of Helsinki. Generally, we suggest authors follow the lead investigator's national standard. If doubt exists whether the research was conducted in accordance with the above standards, the authors must explain the rationale for their approach and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study.

Before submitting, authors should make their study approved by the relevant research ethics committee or institutional review board. If human participants were involved, manuscripts must be accompanied by a statement that the experiments were undertaken with the understanding and appropriate informed consent of each. Any personal item or information will not be published without explicit consents from the involved patients. If experimental animals were used, the materials and methods (experimental procedures) section must clearly indicate that appropriate measures were taken to minimize pain or discomfort, and details of animal care should be provided.

SUBMISSION OF MANUSCRIPTS

Manuscripts should be typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Number all pages consecutively, and start each of the following sections on a new page: Title Page, Abstract, Introduction, Materials and Methods, Results, Discussion, Acknowledgements, References, Tables, Figures, and Figure Legends. Neither the editors nor the publisher are responsible for the opinions expressed by contributors. Manuscripts formally accepted for publication become the permanent property of Baishideng Publishing Group Co., Limited, and may not be reproduced by any means, in whole or in part, without the written permission of both the authors and the publisher. We reserve the right to copy-edit and put onto our website accepted manuscripts. Authors should follow the relevant guidelines for the care and use of laboratory animals of their institution or national animal welfare committee. For the sake of transparency in regard to the performance and reporting of clinical trials, we endorse the policy of the ICMJE to refuse to publish papers on clinical trial results if the trial was not recorded in a publicly-accessible registry at its outset. The only register now available, to our knowledge, is <http://www.clinicaltrials.gov> sponsored by the United States National Library of Medicine and we encourage all potential contributors to register with it. However, in the case that other registers become available you will be duly notified. A letter of recommendation from each author's organization should be provided with the contributed article to ensure the privacy and secrecy of research is protected.

Authors should retain one copy of the text, tables, photographs and illustrations because rejected manuscripts will not be returned to the author(s) and the editors will not be responsible for loss or damage to photographs and illustrations sustained during mailing.

Online submissions

Manuscripts should be submitted through the Online Submission System at: <http://www.wjgnet.com/esp/>. Authors are highly recommended to consult the ONLINE INSTRUCTIONS TO AUTHORS (http://www.wjgnet.com/2220-3230/g_info_20100722180909.htm) before attempting to submit online. For assistance, authors encountering problems with the Online Submission System may send an email describing the problem to wjt@wjgnet.com, or by telephone: +86-10-85381892. If you submit your manuscript online, do not make a postal contribution. Repeated online submission for the same manuscript is strictly prohibited.

MANUSCRIPT PREPARATION

All contributions should be written in English. All articles must be submitted using word-processing software. All submissions must be typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Style should conform to our house format. Required information for each of the manuscript sections is as follows:

Title page

Title: Title should be less than 12 words.

Running title: A short running title of less than 6 words should be provided.

Authorship: Authorship credit should be in accordance with the standard proposed by ICMJE, based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

Institution: Author names should be given first, then the complete name of institution, city, province and postcode. For example, Xu-Chen Zhang, Li-Xin Mei, Department of Pathology, Chengde Medical College, Chengde 067000, Hebei Province, China. One author may be represented from two institutions, for example, George Sgourakis, Department of General, Visceral, and Transplantation Surgery, Essen 45122, Germany; George Sgourakis, 2nd Surgical Department, Korgialenio-Benakio Red Cross Hospital, Athens 15451, Greece

Author contributions: The format of this section should be: Author contributions: Wang CL and Liang L contributed equally to this work; Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed the research; Wang CL, Zou CC, Hong F and Wu XM performed the research; Xue JZ and Lu JR contributed new reagents/analytic tools; Wang CL, Liang L and Fu JF analyzed the data; and Wang CL, Liang L and Fu JF wrote the paper.

Supportive foundations: The complete name and number of supportive foundations should be provided, e.g. Supported by National Natural Science Foundation of China, No. 30224801

Correspondence to: Only one corresponding address should be provided. Author names should be given first, then author title, affiliation, the complete name of institution, city, postcode, province, country, and email. All the letters in the email should be in lower case. A space interval should be inserted between country name and email address. For example, Montgomery Bissell, MD, Professor of Medicine, Chief, Liver Center, Gastroenterology Division, University of California, Box 0538, San Francisco, CA 94143, United States. montgomerybissell@ucsf.edu

Telephone and fax: Telephone and fax should consist of +, country number, district number and telephone or fax number, e.g. Telephone: +86-10-85381892 Fax: +86-10-85381893

Peer reviewers: All articles received are subject to peer review. Normally, three experts are invited for each article. Decision for acceptance is made only when at least two experts recommend an article for publication. Reviewers for accepted manuscripts are acknowledged in each manuscript, and reviewers of articles which were not accepted will be acknowledged at the end of each issue. To ensure the quality of the articles published in *WJT*, reviewers of accepted manuscripts will be announced by publishing the name, title/position and institution of the reviewer in the footnote accompanying the printed article. For example, reviewers: Professor Jing-Yuan Fang, Shanghai Institute of Digestive Disease, Shanghai, Affiliated Renji Hospital, Medical Faculty, Shanghai Jiaotong University, Shanghai, China; Professor Xin-Wei Han, Department of Radiology, The First Affiliated Hospital, Zhengzhou University, Zhengzhou, Henan Province, China; and Professor Anren Kuang, Department of Nuclear Medicine, Huaxi Hospital, Sichuan University, Chengdu, Sichuan Province, China.

Abstract

There are unstructured abstracts (no more than 256 words) and structured abstracts (no more than 480). The specific requirements for structured abstracts are as follows:

An informative, structured abstracts of no more than 480 words should accompany each manuscript. Abstracts for original contributions should be structured into the following sections. AIM (no more than 20 words): Only the purpose should be included. Please write the aim as the form of "To investigate/study/...; MATERIALS AND METHODS (no more than 140 words); RESULTS (no more than 294 words): You should present *P* values where appropriate and must provide relevant data to illustrate how they were obtained, e.g. 6.92 ± 3.86 vs 3.61 ± 1.67 , $P < 0.001$; CONCLUSION (no more than 26 words).

Key words

Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

Text

For articles of these sections, original articles and brief articles, the main text should be structured into the following sections: INTRODUCTION, MATERIALS AND METHODS, RESULTS and DISCUSSION, and should include appropriate Figures and Tables. Data should be presented in the main text or in Figures and Tables, but not in both. The main text format of these sections, editorial, topic highlight, case report, letters to the editors, can be found at: http://www.wjgnet.com/2220-3230/g_info_20100725072755.htm.

Illustrations

Figures should be numbered as 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each figure on a separate page. Detailed legends should not be provided under the figures. This part should be added into the text where the figures are applicable. Figures should be either Photoshop or Illustrator files (in tiff, eps, jpeg formats) at high-resolution. Examples can be found at: <http://www.wjgnet.com/1007-9327/13/4520.pdf>; <http://www.wjgnet.com/1007-9327/13/4554.pdf>; <http://www.wjgnet.com/1007-9327/13/4891.pdf>; <http://www.wjgnet.com/1007-9327/13/4986.pdf>; <http://www.wjgnet.com/1007-9327/13/4498.pdf>. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. File names should identify the figure and panel. Avoid layering type directly over shaded or textured areas. Please use uniform legends for the same subjects. For example: Figure 1 Pathological changes in atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ... *etc.* It is our principle to publish high resolution-figures for the printed and E-versions.

Tables

Three-line tables should be numbered 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each table. Detailed legends should not be included under tables, but rather added into the text where applicable. The information should complement, but not duplicate the text. Use one horizontal line under the title, a second under column heads, and a third below the Table, above any footnotes. Vertical and italic lines should be omitted.

Notes in tables and illustrations

Data that are not statistically significant should not be noted. ^a*P* < 0.05, ^b*P* < 0.01 should be noted (*P* > 0.05 should not be noted). If there are other series of *P* values, ^c*P* < 0.05 and ^d*P* < 0.01 are used. A third series of *P* values can be expressed as ^e*P* < 0.05 and ^f*P* < 0.01. Other notes in tables or under illustrations should be expressed as ¹F, ²F, ³F; or sometimes as other symbols with a superscript (Arabic numerals) in the upper left corner. In a multi-curve illustration, each curve should be labeled with ●, ○, ■, ▲, △, *etc.*, in a certain sequence.

Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

REFERENCES

Coding system

The author should number the references in Arabic numerals according to the citation order in the text. Put reference numbers in square brackets in superscript at the end of citation content or after the cited author's name. For citation content which is part of the narration, the coding number and square brackets should be typeset normally. For example, "Crohn's disease (CD) is associated with increased intestinal permeability^[1,2]". If references are cited directly in the text, they should be put together within the text, for example, "From references^[19,22-24], we know that..."

When the authors write the references, please ensure that the order in text is the same as in the references section, and also ensure the spelling accuracy of the first author's name. Do not list the same citation twice.

PMID and DOI

Please provide PubMed citation numbers to the reference list, e.g. PMID and DOI, which can be found at <http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed> and <http://www.crossref.org/SimpleTextQuery/>, respectively. The numbers will be used in E-version of this journal.

Style for journal references

Authors: the name of the first author should be typed in bold-faced letters. The family name of all authors should be typed with the initial letter capitalized, followed by their abbreviated first and middle initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR). The title of the cited article and italicized journal title (journal title should be in its abbreviated form as shown in PubMed), publication date, volume number (in black), start page, and end page [PMID: 11819634 DOI: 10.3748/wjg.13.5396].

Style for book references

Authors: the name of the first author should be typed in bold-faced letters. The surname of all authors should be typed with the initial letter capitalized, followed by their abbreviated middle and first initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR) Book title. Publication number. Publication place: Publication press, Year: start page and end page.

Format

Journals

English journal article (list all authors and include the PMID where applicable)

- 1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

- 2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

- 3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

- 4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMID: 2516377 DOI: 10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

- 5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI: 10.1097/01.ju.0000067940.76090.73]

No author given

- 6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI: 10.1136/bmj.325.7357.184]

Volume with supplement

- 7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI: 10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

- 8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; **(401)**: 230-238 [PMID: 12151900 DOI: 10.1097/00003086-200208000-00026]

No volume or issue

- 9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

- 10 **Sherlock S**, Dooley J. Diseases of the liver and biliary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

- 11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

- 12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wiczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

- 13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

- 14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

- 15 Morse SS. Factors in the emergence of infectious diseases. *Emerg Infect Dis* serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: <http://www.cdc.gov/ncidod/eid/index.htm>

Patent (list all authors)

- 16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean \pm SD or mean \pm SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as *v* (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, *m* (B) = 78 kg; blood pressure, *p* (B) = 16.2/12.3 kPa; incubation time, *t* (incubation) = 96 h; blood glucose concentration, *c* (glucose) 6.4 \pm 2.1 mmol/L; blood CEA mass concentration, *p* (CEA) = 8.6 24.5 μ g/L; CO₂ volume fraction, 50 mL/L CO₂, not 5% CO₂; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, etc. Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantities can be found at: http://www.wjgnet.com/2220-3230/g_info_20100725073806.htm.

Abbreviations

Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.

Genotypes: *gyrA*, *arg 1*, *c myc*, *c fos*, etc.

Restriction enzymes: *EcoRI*, *HindI*, *BamHI*, *Kho I*, *Kpn I*, etc.

Biology: *H. pylori*, *E. coli*, etc.

Examples for paper writing

Editorial: http://www.wjgnet.com/2220-3230/g_info_20100725071851.htm

Frontier: http://www.wjgnet.com/2220-3230/g_info_20100725071932.htm

Topic highlight: http://www.wjgnet.com/2220-3230/g_info_20100725072121.htm

Observation: http://www.wjgnet.com/2220-3230/g_info_20100725072232.htm

Guidelines for basic research: http://www.wjgnet.com/2220-3230/g_info_20100725072344.htm

Guidelines for clinical practice: http://www.wjgnet.com/2220-3230/g_info_20100725072543.htm

Review: http://www.wjgnet.com/2220-3230/g_info_20100725072656.htm

Original articles: http://www.wjgnet.com/2220-3230/g_info_20100725072755.htm

Brief articles: http://www.wjgnet.com/2220-3230/g_info_20100725072920.htm

Case report: http://www.wjgnet.com/2220-3230/g_info_20100725073015.htm

Letters to the editor: http://www.wjgnet.com/2220-3230/g_info_20100725073136.htm

Book reviews: http://www.wjgnet.com/2220-3230/g_info_20100725073214.htm

Guidelines: http://www.wjgnet.com/2220-3230/g_info_20100725073300.htm

SUBMISSION OF THE REVISED MANUSCRIPTS AFTER ACCEPTED

Authors must revise their manuscript carefully according to the revision policies of Baishideng Publishing Group Co., Limited. The revised version, along with the signed copyright transfer agreement, responses to the reviewers, and English language Grade B certificate (for non-native speakers of English), should be submitted to the online system *via* the link contained in the e-mail sent by the editor. If you have any questions about the revision, please send e-mail to esps@wjgnet.com.

Language evaluation

The language of a manuscript will be graded before it is sent for revision. (1) Grade A: priority publishing; (2) Grade B: minor language polishing; (3) Grade C: a great deal of language polishing needed; and (4) Grade D: rejected. Revised articles should reach Grade A or B.

Copyright assignment form

Please download a Copyright assignment form from http://www.wjgnet.com/2220-3230/g_info_20100725073726.htm.

Responses to reviewers

Please revise your article according to the comments/suggestions provided by the reviewers. The format for responses to the reviewers' comments can be found at: http://www.wjgnet.com/2220-3230/g_info_20100725073445.htm.

Proof of financial support

For paper supported by a foundation, authors should provide a copy of the document and serial number of the foundation.

Links to documents related to the manuscript

WJT will be initiating a platform to promote dynamic interactions between the editors, peer reviewers, readers and authors. After a manuscript is published online, links to the PDF version of the submitted manuscript, the peer-reviewers' report and the revised manuscript will be put on-line. Readers can make comments on the peer reviewer's report, authors' responses to peer reviewers, and the revised manuscript. We hope that authors will benefit from this feedback and be able to revise the manuscript accordingly in a timely manner.

Science news releases

Authors of accepted manuscripts are suggested to write a science news item to promote their articles. The news will be released rapidly at EurekAlert/AAAS (<http://www.eurekalert.org>). The title for news items should be less than 90 characters; the summary should be less than 75 words; and main body less than 500 words. Science news items should be lawful, ethical, and strictly based on your original content with an attractive title and interesting pictures.

Publication fee

WJT is an international, peer-reviewed, OA, online journal. Articles published by this journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license. Authors of accepted articles must pay a publication fee. Publication fee: 600 USD per article. Editorial, topic highlights, book reviews and letters to the editor are published free of charge.