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Progress and Paradigms in Multiple Myeloma

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Abstract

Remarkable progress has been achieved in multiple myeloma, and patient median survival has been extended three to four fold. Specifically, there are 16 new approved treatments for multiple myeloma (MM) in the past 12 years, including 7 in 2015, and the treatment paradigm and patient outcome have been transformed. The definitions of patients benefitting from these therapies has been broadened. Response criteria now include minimal residual disease (MRD), assessed in bone marrow by multicolor flow cytometry or sequencing, and by imaging for extramedullary disease. Initial therapy for transplant candidates is a triplet incorporating novel therapies, ie lenalidomide bortezomib dexamethasone or cytoxan bortezomib dexamethasone. Lenalidomide maintenance until progression can prolong progression free and overall survival in standard risk MM, with incorporation of proteasome inhibitor for high risk disease. Studies are evaluating the value of early versus late transplant and MRD as a therapeutic goal to inform therapy. In non-transplant patients triplet therapies are also preferred, with doublet therapy reserved for frail patients, and maintenance as described above. The availability of second generation proteasome inhibitors (carfilzomib, ixazomib), immunomodulatory drugs (pomalidomide), histone deacetylase inhibitors (panobinostat), and monoclonal antibodies (elotuzumab, daratumumab) allows for effective combination therapies of relapsed disease as well. Finally, novel therapies targeting protein degradation, restoring autologous memory anti-MM immunity, and exploiting genetic vulnerabilities show promise to improve patient outcome even further.

Introduction

Over the last four decades, remarkable progress has been made in our understanding of the biology and pathogenesis of plasma cell dyscrasias. These advances have translated to evolving definitions of disease and prognosis; more stringent criteria for response; transformation of the treatment paradigm integrating stem cell transplantation, targeted, and immune therapies; and most importantly, increased extent and frequency of response associated with three to four fold prolongation of median survival (1–4; Fig. 1.) Indeed subsets of patients with favorable genetic profiles now have a chronic disease with functional cure. This *CCR Focus* will highlight the landmarks of progress in disease biology and clinical practice, and provide a roadmap for even further progress.

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Definition of the disease

As detailed by Landgren and Rajkumar (5), the definition of multiple myeloma (MM) has traditionally included excess monoclonal bone marrow (BM) plasma cells in the setting of monoclonal protein in blood and/or urine, and treatment was initiated only in the setting of disease-related manifestations including hypercalcemia, renal dysfunction, anemia or bone disease (CRAB). Individuals at earlier stages in the spectrum of plasma cell dyscrasias, namely monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) with lower amounts of monoclonal protein and BM plasma cells, were followed without therapy. At present patients with MGUS are monitored expectantly, as overall only 1% individuals per year will develop MM or a related lymphoproliferative disease; within MGUS, non IgG monoclonal protein, monoclonal protein >1.5gm/dL and abnormal kappa:lambda ratio can further refine risk of progression (6). Importantly, a recent study has led to the redefinition and extension of which patients with MM can benefit from therapy. In particular, a recent trial compared lenalidomide and dexamethasone versus no therapy in patients with SMM and showed prolongation of both progression free survival (PFS) and overall survival (OS) in the treated cohort (7). For there to be an OS difference with short followup, some of these patients with SMM progressed very rapidly to active MM. Based on analysis of the subset of SMM with rapid progression, the International Myeloma Working Group (IMWG) has therefore now redefined patients with active MM who can benefit from therapy to include those with >60% BM plasma cells, kappa:lambda ratio >100, and more than one bone lesion on total body MRI or PET/CT scan, even in the absence of CRAB (8). Correspondingly, SMM now includes patients with >3gm/dL serum monoclonal protein, 10–60% monoclonal BM plasma cells, and absence of bone disease on MRI or PET/CT scan. Although the standard of practice is no therapy for patients with SMM, targeted and immune therapies used to treat active disease are well tolerated with a favorable therapeutic index. Therefore multiple protocols of targeted and immune therapies are now ongoing treating patients earlier in the disease course to delay or prevent progression of SMM to active disease requiring therapy. For example, a peptide-based vaccine targeting SLAMF-7, CD138, and XBP-1 in patients with SMM can generate an autologous immune anti-MM response, which can be enhanced and shifted to memory response by lenalidomide or histone deacetylase 6 inhibitor (9–11). This early experience suggests that it may be possible to vaccinate patients, even at the MGUS phase, and generate an autologous memory anti-MM response which will prevent progression to disease requiring therapy.

Definitions of response

As novel single agent and combination therapies have improved and achieved increased extent and frequency of response in MM, the definitions of response have similarly evolved. For example, complete response (CR) previously required absence of monoclonal protein by immunofixation; a stringent CR in addition required normal kappa:lambda ratio. More recently, the IMWG has incorporated multicolor flow immunofluorescence flow cytometry and gene sequencing with sensitivity of up to 10^{-6} into MM response criteria, as well as absence of bone disease on more sensitive imaging including MRI and PET/CT scanning (12). Recent meta-analyses and randomized trials are defining absence of minimal residual

disease (MRD) using these metrics (13,14). For example, early analyses from our trial of lenalidomide, bortezomib, and dexamethasone followed by early versus late high dose therapy and autologous stem cell transplant and one year of lenalidomide maintenance therapy shows that gene sequencing may be more sensitive than multicolor flow cytometry for detecting MRD and predicting outcome (15). Additional ongoing studies and more followup are necessary to achieve the important goal of defining the regulatory and clinical utility of MRD. Indeed initial combination targeted therapy with or without transplant now achieves PFS of many years, highlighting the urgent need to establish the utility of MRD at earlier time points to predict PFS and OS, so that it can be used an endpoint in clinical trials for regulatory approval. Whether MRD negativity should be a goal of therapy for newly diagnosed or relapsed MM, and whether duration of maintenance therapy can be informed by MRD status are among the important patient management issues now being addressed in clinical trials. Already patient and study level meta-analyses of available studies show that MRD negativity portends longer PFS and OS (14), and will soon likely be incorporated in regulatory approval processes of novel agents and medical practice in MM. Finally, rapid progress in novel technologies for measuring MRD include single MM cell gene sequencing and serum cell free DNA, “liquid biopsies” which may make it possible to more accurately and readily measure MRD (16,17).

Genetic and molecular pathogenesis: prognostic and therapeutic implications

Our understating of the genetic and molecular pathogenesis of MM has similarly rapidly advanced. Early genomic profiling studies characterized changes associated with progression from MGUS to SMM to active MM, showing that many hallmark abnormalities are present even at the MGUS phase (18). More recent genomic studies involving large numbers of clinically-annotated patient samples have delineated heterogeneity and clonality at time of diagnosis and relapse of MM; defined mechanisms of sensitivity or resistance to targeted therapies; identified novel targets; and allowed for individualized treatments (19–22). In this *CCR Focus*, Szalat and colleagues (23) will detail these complexities and describe the utility of genomic profiling in clinical practice today, as well as prospects for precision medicine in MM in the future.

Prognostication in MM has evolved in parallel with the development of more effective therapies. Traditionally the International Staging System (ISS) of the IMWG has staged patients based upon serum $\beta 2$ micoglobulin and albumin, as these parameters are readily and universally obtainable. Correlation of Fluorescent in-situ hybridization (FISH) analyses with clinical outcome has identified standard risk MM with t (11;14) translocation and hyperdiploidy, versus high risk MM with t(4;14), t(14;16), t(14;20), del(17p), and del(13q14). Most recently, the the IMWG has incorporated FISH into the ISS (24). Importantly, the definitions of standard versus high risk disease are continuing to evolve with improved therapies. For example, bortezomib can overcome the adverse prognosis conferred by t(4;14) in patients treated with conventional chemotherapy (25). Pomalidomide and monoclonal antibodies (MoAbs) elotuzumab and daratumumab can achieve responses even in the context of del (17p) (26). As MM progresses, the majority of patients acquire

high risk genetic features, from evolution and/or expansion of most resistant clones. Patterns of clonal changes observed at the time of relapse compared to diagnosis include no change, linear evolution, differential clonal response, or branching evolution (21). These changes are related to intrinsic genomic changes, as well as the influence of the tumor microenvironment and treatment. Most importantly combinations of targeted agents with different mechanisms of action including proteasome inhibitors (PI) with immunomodulatory drugs (IMiDs) (27–29), PIs with histone deacetylase (HDAC) inhibitors (30, 31), and IMiDs with MoAbs (32–34) can overcome these adverse features and achieve durable responses. For example, high risk 17p(p53) deletion MM can respond to second generation IMiD pomalidomide, second generation PI carfilzomib or the combination; and daratumumab achieves responses as a single agent and in combination with IMiDs or PIs in multiply relapsed far advanced disease. As combination targeted and immune therapies now come into routine clinical practice in MM, we will need in an ongoing fashion to define which patient subgroups benefit from particular therapies; and conversely, which patients remain high risk and in need of new options. Since MM is an orphan disease and is itself very heterogeneous, international registries of genomically-profiled and clinically-annotated patient databases will be necessary in order to ultimately provide the most effective combination therapies to individual patients at distinct time points in their disease course.

Although we and others are attempting to selectively target mutations, ie BRAF (35), and pathways, ie MEK or ERK (36), in MM, the heterogeneity and complexity of genetic abnormalities and multi-clonality right from diagnosis, coupled with ongoing DNA damage, are major obstacles to the goal of precision medicine in MM. As noted above, MM is a heterogeneous orphan disease, and pooling of large amounts of genomically-profiled and clinically-annotated data will be necessary to better define patient subsets and inform therapy targeting genetic abnormalities/pathways intrinsic to the tumor cell, and such efforts are now ongoing. We are also undertaking an alternative strategy directed to target the biologic sequelae of the constitutive and ongoing genetic instability and DNA damage in MM. For example, MM cells with decreased YAP1 copy number do not die despite constitutive and ongoing DNA damage; in this subset, genetic deletion of STK4 restores YAP-1 expression and P73 mediated-apoptosis, even in the setting of p53 deleted MM (37; Fig. 2). These studies provide the rationale for the first kinase inhibitor trial targeting STK4 in this subset of patients with MM. We have also shown that MM cells with amplification of Myc have very high levels of replicative stress and reactive oxygen species (ROS) (38); our preclinical studies show that combining agents which block stress response, ie ATR inhibitor, with those enhancing ROS, ie bortezomib, achieves synergistic cytotoxicity, setting the stage for combination clinical trials in this poor prognosis MM subset. Finally, we and others are now attempting to target not only individual genetic abnormalities, but also aberrant regulatory loops in MM. For example, we have recently shown that increased KDM3A demethylase activity in MM allows for transcriptional activation of the IRF4-KLF2 axis in MM, of central importance due to their hallmark role promoting homing of MM cells to the BM and MM cell survival. Conversely, targeting increased KDM3A demethylase activity restores methylation of the IRF4 and KLF2 promoters and suppresses related gene transcription, thereby inhibiting MM cell survival (39). These examples suggest the

promising therapeutic potential of targeting biologic consequences of genomic/epigenomic abnormalities in MM.

Evolution of therapy in MM

The modern history of therapy in MM begins with melphalan and prednisone in the 1960s and evolved to combination therapy in the 1970s. High dose therapy followed by bone marrow and then peripheral blood stem cell rescue were major advances in the 1980s and 1990s which extended median PFS to 4 to 5 years. Since the late 1990s there has been a revolution in MM therapy with the development of PIs bortezomib (40), carfilzomib (41), ixazomib (42), and marizomib (43); IMiDs lenalidomide and pomalidomide (44–47); MoAbs, elotuzumab and daratumumab (32–34); and HDAC inhibitor panobinostat (30). These advances are the direct result of collaborative bench to bedside translational studies involving academia, pharmaceutical industry, regulatory authorities, NIH and Foundation funding sources, and patient advocacy organizations. Over the past 4 decades, we and others have developed laboratory and animal models of MM in the BM which have identified molecular and biologic mechanisms mediating tumor growth, survival, and drug resistance; and also been useful to validate novel targeted therapies (48–53). These fundamental studies both enhanced our understanding of MM pathogenesis and provided novel targets for drug discovery and development including cell surface antigens and receptors (54–56), signaling cascades (57–61), cytokines (62), and BM accessory cells (63–66). Importantly, this pioneering work validated targeting the symbiotic heterotypic interactions between the tumor cell and its microenvironment to overcome drug resistance and improve patient outcome. PIs and IMiDs are the prototype drug classes targeting the MM cell, tumor cell interaction with the BM, and the BM microenvironment, and MM now represents a model for the therapeutic importance of targeting the tumor cell in its microenvironment.

To date these studies have translated to clinical trials resulting in 18 new FDA approved regimens which have transformed the treatment paradigm. Although novel agents are often initially evaluated in patients with relapsed and refractory MM, their regulatory approval and clinical use now extends to newly diagnosed and relapsed MM, as well as for maintenance therapy. Moreover, scientifically-informed combination therapies (lenalidomide, bortezomib, and dexamethasone) have achieved unprecedented extent and frequency of durable responses and have established a new standard-of-care. These remarkable advances, and integration of these novel therapies into clinical practice, will be detailed by Orłowski and Lonial (67) in this *CCR Focus*.

Therapies targeting protein homeostasis

A hallmark advance in MM was the preclinical and clinical development of the PI bortezomib in MM (68–73). Its use was initially predicated upon blocking the degradation of IKB, preventing its dissociation from the NFkB subunits, and thereby blocking NFkB activation in MM. Inhibiting NFkB was thought to be key, given that it mediates survival and drug resistance in MM, modulates adhesion molecules on the tumor cell and in the microenvironment, and regulates transcription of MM growth and survival cytokines in the BM milieu. Subsequently it has been shown to have multiple effects on MM cells including

inducing ROS, triggering unfolded protein and stress responses, targeting cell cycle, and triggering apoptosis; as well as in the microenvironment including inducing osteoclast apoptosis and inhibiting angiogenesis. Through collaborative studies it was rapidly translated to approval and use in relapsed and refractory MM, newly diagnosed disease, and as maintenance therapy, thereby establishing proof-of-principle for therapeutic targeting of protein degradation in MM and other cancers.

Although bortezomib is now incorporated into multiple initial, relapse, and maintenance regimens in MM, development of resistance to bortezomib is common, and our and other efforts are now focusing on delineating and targeting alternative mechanisms modulating protein homeostasis. Second-generation PIs (carfilzomib (41), ixazomib (42), marizomib (43) have now been preclinically and clinically validated (Fig. 3). Carfilzomib is an epoxyketone irreversible covalent PI without significant neurologic toxicity, which is approved alone and with lenalidomide to treat relapsed MM (39). Ixazomib is an oral next-generation boronic acid based PI which targets chymotryptic activity and can overcome bortezomib resistance; combined with lenalidomide and dexamethasone, it is approved to treat relapsed MM and an effective all oral PI and IMiD regimen for newly diagnosed MM (42,74–76). Marizomib is a broad PI which targets chymotryptic, tryptic, and caspase activities, which in preclinical studies can overcome Bortezomib resistance and has now translated to combination clinical trials with pomalidomide (43,77).

We are attempting to overcome PI resistance using two strategies. First, we have shown in preclinical studies that targeting the (UPS) upstream of the proteasome at the level of the ubiquitin proteasome receptor or the deubiquitylating enzymes (DUBs) can overcome PI resistance (Fig. 3). For example, we have defined the functional role of DUBs USP7 (78) and USP14/UCHL5 (79) and ubiquitin receptor Rpn13 (80) in MM, shown that targeted inhibitors can overcome PI resistance, and translated these studies to a clinical trial of b-AP15/VLX 1570 targeting USP14/UCHL5 in MM. Second, we have delineated mechanisms of the alternative aggresomal mechanism of protein degradation and shown that it is upregulated upon proteasome inhibition. Our preclinical studies combining non-selective HDAC inhibitors vorinostat and panobinostat to block aggresomal degradation, together with bortezomib to block proteasomal degradation, triggered accumulation of ubiquitinated proteins and overcame PI resistance (81), setting the stage for derived clinical trials and approval of panobinostat with bortezomib to treat relapsed refractory MM (30). Since HDAC 6 binds to ubiquitinated protein on the one hand and to dynein motility complexes on the other shuttling ubiquitinated protein to the aggresome for degradation, we developed and translated selective HDAC6 inhibitors to promising combination clinical trials in relapsed refractory MM, with improved tolerability relative to more broad HDAC inhibitors (82).

Finally, IMiDs target cereblon (CRN) ubiquitin 3 ligase complex, resulting in the degradation of IZF1/3 and hallmark IRF4 and c-Myc in MM (83,84). Based upon this principle, we are now synthesizing degronimids, agents which both bind and activate ubiquitin 3 ligases and link to substrates, thereby allowing for proteasomal degradation of selective hallmark pathogenic proteins in cancer and other diseases (85).

Immune therapies in MM

Immune strategies to overcome drug resistance in MM will be described by Kumar and Anderson (86) in this *CCR Focus*. Immune therapies in MM now currently include IMiDs, MoAb-based therapies (Fig. 4), checkpoint inhibitors, HDAC inhibitors, vaccines, and cellular therapies. IMiDs directly trigger MM cell apoptosis, abrogate tumor cells adhesion to the BM, modulate cytokines, and inhibit angiogenesis; as well as augment T cell, NK cell, and NK-T cell function, while downregulating T regulatory cells (87–89). Binding to CRBN has been implicated in both direct cytotoxic and immune-related effects of IMiDs. Importantly, they augment antibody dependent cellular cytotoxicity and clinical activity of MoAbs, and elotuzumab targeting SLAMF-7 is approved with lenalidomide to treat relapsed refractory MM (32, 54). MM cells, as well as myeloid derived suppressor cells (MDSCs) and plasmacytoid dendritic cells (pDCs) which augment MM cell growth and suppress host immune function, express PD-L1 (63–65); whereas immune effector T and NK cells express PD-1. Checkpoint blockade can induce MM cell specific CD4 and CD8 cytolytic T cells (CTLs) as well as NK cell cytotoxicity even in the presence of MDSCs and pDCs, thereby inhibiting MM cell growth in the BM milieu (65). Early studies show clinical efficacy of lenalidomide with PD-1 blockade (90). In preclinical studies HDAC6 inhibitor can augment autologous MM cytotoxicity and add to MoAb and PD-L1 antibody. Peptide based vaccine strategies are being evaluated to target multiple tumor-associated antigens on MM cells and block progression of SMM to active disease (9–11); and MM cell/DC fusion vaccines are being evaluated to treat minimal residual disease posttransplant and improve outcome (91). In both cases MM specific T cell immune responses have been triggered by vaccination, which can be increased by lenalidomide (90); already a randomized trial is comparing lenalidomide versus lenalidomide plus MM cell/DC fusion vaccine posttransplant is ongoing. Excitingly, combination of vaccination with checkpoint inhibitors and HDAC6 inhibitor can promote effector and memory T cell function and increased anti-MM immunity, evidenced by cytotoxic activities; trigger production of Th1-type of cytokines (IFN- γ , IL-2, TNF- α); and induce costimulatory/activation molecules. Their potential role for epitope spreading to allow for targeting additional tumor-associated antigens and enhance anti-tumor cytotoxic activities is under investigation. Finally, CAR T cells and other strategies including immunotoxins, bispecific MoAbs, and CAR T cells targeting BCMA have demonstrated preclinical activity and early clinical promise (56, 92). In the future it is likely that combinations of immune approaches including IMiDs, MoAbs, checkpoint inhibitors, HDAC inhibitors, vaccines, and/or cellular therapies will confer long-lasting anti-MM immunity and durable response.

Conclusions

Remarkable progress in MM has been achieved in the past two decades, particularly due to integration of stem cell transplantation with novel therapies including IMiDs and PIs. Most recently, the advent of MoAbs has provided effective therapy even in multiply relapsed disease. Importantly, combination IMiD, PI, and MoAb regimens are now being evaluated earlier in the disease course, and will have even greater efficacy as initial therapy. The future is even more exciting. The three Achilles heels or vulnerabilities to exploit in novel therapeutics include blocking protein degradation, restoring anti-MM immunity, and

targeting the consequences of the constitutive genetic complexity and ongoing DNA damage, as described above. On the one hand, scientific advances will continue to increase our basic understanding and therapeutic armamentarium, allowing for clinical trials of precision medicine in MM. Although these trials are promising, it may be difficult to target multiple, continually evolving, clonal and genetic abnormalities in the right combination at the right time and in the correct sequence. That is why targeting the consequences of this ongoing DNA damage, such as blocking stress responses in MM cells, offers great appeal. On the other hand, immune therapies are selective, adaptable, and potent, and offer great promise to overcome ongoing genomic instability underlying relapse in MM. As described above, the immune-based therapies in MM now include IMiDs, MoAbs, checkpoint inhibitors, HDAC6 inhibitors, vaccines, and cellular therapies. Importantly, preclinical and early clinical trials suggest the potency of combinations, such as IMiDs with MoAbs, IMiDs with checkpoint inhibitors, IMiDs with HDAC6 inhibitors, and vaccines with IMiDs. Particularly exciting is early evidence that vaccinating patients with SMM can induce an autologous anti-MM selective response, which can be augmented and be of central and effector memory type in the presence of IMiDs and HDAC6 inhibitors. Ultimately, combinations of immune therapies used early in the disease course, now in SMM and in the future in MGUS, may achieve long-term memory anti-MM immunity which will prevent progression to active MM ever requiring therapy.

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Figure 1. Bench to Bedside Translation of Novel Agents in Myeloma

Early advances in myeloma therapy included melphalan and prednisone, followed by combination chemotherapy and then high dose melphalan, rescued first by bone marrow and more recently by peripheral blood stem cell transplantation. Importantly, remarkable progress has been made in the last twelve years due to the FDA approval of proteasome inhibitors bortezomib, carfilzomib, and ixazomib; immunomodulatory drugs thalidomide, lenalidomide, and pomalidomide; histone deacetylase inhibitor panobinostat; as well as monoclonal antibodies elotuzumab and daratumumab (left). All these recent therapies have been initially evaluated and achieved responses in relapsed refractory MM, and then moved into clinical trials earlier in the disease course where their efficacy improves. Moreover, their use in combination, ie lenalidomide, bortezomib, and dexamethasone, can achieve unprecedented frequency and extent of response when used as initial therapy. They have been integrated into the treatment paradigm of transplant candidates and non-transplant candidates as initial and as maintenance therapies. As a consequence of these advances, overall survival has been extended from a median of 3 to 8–10 years (4), and the benefit of most recently approved drugs will further improve outcome (right).

Figure 2. Restoring Apoptotic Signaling By Serine Threonine Kinase Inhibitor in YAP1-Deficient Multiple Myeloma

A subset of patients with myeloma, lymphoma, and leukemia have decreased copy number and expression of YAP1 (37). As a result, these tumor cells with ongoing DNA damage do not undergo apoptosis (left). Serine threonine kinase (STK) 4 inhibits expression of YAP1; conversely, genetic or pharmacologic inhibition of STK4 allows re-expression of YAP1 and downstream p73-mediated apoptosis of these tumor cells with ongoing DNA damage to occur (right). Adapted from ref. 37.

Figure 3. Targeting Ubiquitin Proteasome System

Multiple proteasome inhibitors including bortezomib, carfilzomib, ixazomib, and oprozomib primarily inhibit the chymotryptic-like proteasome activity, whereas marizomib inhibits chymotryptic-, tryptic-, and caspase-like activities. In the ubiquitin-proteasome cascade of protein degradation, ubiquitin proteasome receptors and deubiquitylating enzymes are upstream of the proteasome and required for recruiting and deubiquitylating ubiquitylated misfolded proteins, respectively, so that they can bind to the 20S core of the proteasome and be degraded. Blockade of either ubiquitin proteasome receptors and deubiquitylating enzymes upstream of the proteasome therefore has the potential to overcome proteasome inhibitor resistance.

Figure 4. Monoclonal Antibody-Based Therapies for Multiple Myeloma

Monoclonal antibodies used therapeutically in MM can trigger antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, block signaling pathways mediating MM cell growth, survival, and drug resistance, or trigger apoptotic signaling cascades. Clinically FDA approved monoclonal antibodies daratumumab and elotuzumab target CD38 and SLAMF-7, respectively. Adapted from ref. 93. © 2011 Yu-Tzu Tai and Kenneth C. Anderson. Published by Hindawi. This is an open access article distributed under the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/3.0/us/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. The article in which the original figure appeared is published with open access at <http://dx.doi.org/10.1155/2011/924058>.