Comment:

Creatine Promotion of Cancer Metastasis: A Critical Evaluation

As leading scholars on creatine supplementation, we read with interest the paper published by Zhang and coworkers (Zhang et al., 2021) reporting that creatine promotes cancer metastasis through activation of Smad2/3 and calling for "*caution when considering dietary creatine to improve muscle mass or treat diseases*" and asserting that "…*and instead (creatine)* ***will*** *promote cancer metastasis*". After reviewing this paper, we wish to dispute whether this cautionary and definitive statement regarding human health is warranted and may unnecessarily mislead and alarm the public.

Creatine is found in gram quantities primarily in meat and fish with an estimated daily intake of 2 – 4 grams required to maintain normal creatine levels in the human body depending on habitual dietary intake (Kreider and Stout, 2021, Wallimann et al., 2011). In 1993, after pioneering creatine research by Dr. Roger Harris (Harris et al., 1992), creatine monohydrate became readily available as a dietary supplement in the United States, in full compliance with the U.S. Food and Drug Administration (FDA). Since creatine is readily found in the food supply and it was available as a dietary supplement prior to October 15th, 1994, it was "grandfathered in" as a legal dietary ingredient that could be lawfully sold in the United States under the Dietary Supplement Health Education Act (DSHEA). It is also an approved substance for inclusion in dietary supplements and/or food products in Canada, Australia, the European Union, Japan, South Korea, Brazil, and other countries (Jager et al., 2011). More recently, the FDA had no objections to a Generally Recognized as Safe (GRAS) application allowing creatine monohydrate to be included as a food additive in various foods (GRN 931). In humans, hundreds of studies (including randomized, double-blind, placebo controlled clinical trials) have shown that creatine monohydrate supplementation is safe and effective (Kreider et al., 2017, Kreider and Stout, 2021). For this reason, there is consensus within the scientific community that creatine monohydrate supplementation (i.e., 20 grams/day for first 5 – 7 days; 3 – 5 grams/day thereafter; 0.1 grams/kg/day) can safely and effectively improve exercise performance capacity and training adaptations in untrained and trained individuals, with and without an exercise intervention (Burke et al., 2019, Candow et al., 2019, Forbes et al., 2021, Kreider et al., 2017, Kreider and Stout, 2021, Kley et al., 2013, Maughan et al., 2018).

There is a strong metabolic basis for the role of creatine in the management of many diseases (Bonilla et al., 2021, Wallimann et al., 2011) and emerging evidence suggests that creatine monohydrate supplementation may possess several health benefits in pregnancy and infancy (Muccini et al., 2021), children and adolescents (Jagim and Kerksick, 2021), women (Smith-Ryan et al., 2021), adults involved in exercise training (Kreider et al., 2017), and older populations (Candow et al., 2019, Candow et al., 2021, Chilibeck et al., 2017, Forbes et al., 2021, Smith-Ryan et al., 2021). Additionally, there is evidence that creatine monohydrate supplementation may enhance immunity (Bredahl et al., 2021) as well as promote heart (Balestrino, 2021), vascular (Clarke et al., 2021), and brain health (Roschel et al., 2021). Therapeutic benefits have been reported in the management of diabetes (Solis et al., 2021), sarcopenia (Candow et al., 2019, Chilibeck et al., 2017, Dolan et al., 2019a, Riesberg et al., 2016), osteoporosis (Candow et al., 2019, Candow et al., 2021), patients with neuromuscular diseases (Tarnopolsky, 2007), rehabilitation (Al-Ghimlas and Todd, 2010, Balestrino et al., 2016, Balestrino and Adriano, 2019, Cornelissen et al., 2010, Dolan et al., 2019a, Dover et al., 2020, Hespel et al., 2001, Hespel and Derave, 2007, Neves et al., 2011), and on cognitive function (Avgerinos et al., 2018, Dolan et al., 2019b, Forbes et al., 2021, Roschel et al., 2021, Toniolo et al., 2017). Data show that creatine and/or creatine analogs slow the progression of some forms of cancer and powers anti-tumor T cell immunity (Bergnes et al., 1996, Campos-Ferraz et al., 2016, Di Biase et al., 2019), may have therapeutic benefit in helping cancer patients maintain muscle mass (Fairman et al., 2019), and may prevent body fat accumulation during maintenance chemotherapy that included corticosteroids (Bourgeois et al., 2008). As a result, creatine monohydrate has become one of the most thoroughly studied and evidence-based dietary supplements today (Jager et al., 2011, Kreider et al., 2017, Kreider and Stout, 2021).

Zhang et al. (2021) reported convincing evidence that creatine monohydrate provided to mice at supraphysiological doses promoted metastasis of cancer cell lines implanted into an animal model. Moreover, the activation of the endogenous creatine synthesis pathway within the cancer cells and oral creatine administered at high doses promoted liver metastases and lowered survival in mice attributed to the enhancement of metastases. While these findings are interesting, it should be noted that they were observed following *orthotropic transplantation* of a human colorectal cancer cell line (HCT116), a patient-derived xenograft cell line (CRC57), as well as mouse colon cancer (CT26) and mouse breast cancer cell lines (4T1), whilst further exposed to supraphysiological levels of creatine. These researchers are the only

group we are aware of that have reported these results (Zhang et al., 2021), although some reports suggest that the phosphagen energy system may, in an atypical manner, play a role in cancer cell metastasis (Papalazarou et al., 2020) and cancer cell survival (Kazak and Cohen, 2020).

The researchers also reported that the expression of arginine-glycine aminotransferase (*AGAT*, or *GATM*), the first of two enzymes for endogenous creatine synthesis, was upregulated with metastases compared to the primary tumors, indicating that metastatic cancer cells upregulated the creatine synthesis pathway. The implied suggestion was that this upregulation was required to improve cellular energetics by building up, via the enzyme creatine kinase (*CK*), higher amounts of phosphorylcreatine (PCr) for buffering the cellular energy charge (Wallimann et al., 2011), required for the formation of metastases. One interpretation, based on the current study is that tumorigenesis/metastases are energetically demanding multifactorial processes involving the break down/remodeling and movement through extracellular matrix (ECM), angiogenesis, and enhanced DNA/protein synthesis for invasion of the target tissue. To achieve this, metastasizing cells adapt their strategies for energy provision and nutrient uptake in many different ways, one of them by upregulation of the CK/PCr system (Garde and Sherwood, 2021) and glucose-driven glycolysis (i.e., Warburg effect). This was also true for the colon and breast cancer cell lines investigated by the authors since they upregulated *AGAT* (*GATM*), the rate-limiting enzyme for creatine synthesis, and by doing so, they were able to promote metastasis on their own, even without externally added creatine (Zhang et al., 2021). However, we feel that the observation of enhanced metastases induced by feeding mice harboring metastasis-competent cancer cells extremely high doses of creatine, is far more likely to be due to a species-specific creatine stimulated alteration of the metastatic tissue microenvironment in the recipient tissue and not specifically the upregulation of the *AGAT* (*GATM*) and guanidinoacetate N-methyltransferase (*GAMT)* pathways and/or creatine induced activation of the Smad2/3 pathway in the primary tumor to induce metastatic capacity. If creatine supplementation *per se* were stimulating the endogenous creatine synthesis pathway it would be expected that this would have also enhanced the growth of the implanted primary tumor cells, and yet the primary tumors displayed anti-proliferative features in the current study with creatine supplementation.

We have several concerns about this study design, report, and conclusions that should be considered:
First, the researchers used a severely immunocompromised, CRISPR/Cas9-modified mouse model, which may have compromised the interpretation of results and application to human cancer models. Specifically, this NCG strain (NOD/ShiLtJGpt-*Prkdc* ^{em26Cd52} *Il2rg* ^{em26Cd22}/Gpt), albeit receptive to the cell and patient derived xenografts used in the study, lacked any humanization elements e.g co-injection of stromal cells (Frese and Tuveson, 2007) or engraftment of human hematopoietic stem and precursor cells (Morton et al., 2016). The absence of an operative tumor surveillance and vigilance system lacks a resemblance to tumor-bearing state in humans. Indeed, one of us (Di Biase et al., 2019), 2019), using a subcutaneous injection model in a similar NSG mouse strain, and in T cell depleted C57BL/6J WT mice, demonstrated the axial role of T cell immunocompetence in mediating the anti-tumor effects of creatine administration.

Second, the amount of creatine supplemented orally, either added to solid food pellets (5% w/w) or given as an aqueous creatine suspension (slurry) by gavage feeding, was much higher than typically consumed by humans. Using standard calculations for a 70 kg individual (Bachmanov et al., 2002), this would be equivalent to consuming about *560 grams/day* of creatine monohydrate in solid food pellets while gavage feeding provided *48 grams* of creatine monohydrate three times per week. Even if the mice, most likely feeling sick due to their cancer pathology, consumed only 10% – 20% of the above mentioned 5% creatine dry food pellets, they would still consume an equivalent of more than 50 – 100 gram/day of creatine for a 70 kg person for a prolonged period until sacrificed. Thus, the doses used in this study were not realistic of the amount of creatine monohydrate humans would consume from dietary supplements (e.g., 3 – 10 grams/day).

Third, there is no evidence at all that creatine supplementation in humans would cause the production of mutagens or carcinogens (Pereira et al., 2015), nor any other purported side effects (Antonio et al., 2021, Kreider et al., 2017, Kreider and Stout, 2021). Moreover, Zhang et al. (2021) found that creatine had an *anti-proliferative* effect on primary tumor growth, in accordance with earlier studies (Campos-Ferraz et al., 2016, Kazak and Cohen, 2020). In fact, as demonstrated by Zhang et al. (2021), the creatine supplemented animals, "…*either did not affect or slightly suppressed primary tumor growth in the cecum*..." and "*Creatine treatment inhibited breast tumor growth in the fat pad*." Creatine has also convincingly been shown to represent an essential metabolic regulator controlling anti-tumor T cell immunity and creatine

supplementation represents a valid strategy in cancer protection and/or management (Di Biase et al., 2019, Fairman et al., 2019). There is also recent evidence that bacteria disrupt the gut vascular barrier, causing bacterial dissemination to the liver and the formation of a premetastatic niche, favoring recruitment of metastatic cells (Murota and Jobin, 2021), and that creatine is paramount for the maintenance of the intestinal barrier which theoretically could benefit patients with colon cancer and inflammatory bowel disease (Wallimann et al., 2021). Furthermore, from an epidemiological perspective, many millions of people have been taking creatine supplements at doses from 3 – 10 grams/day for well over two decades for a variety of reasons (e.g., sport enhancement, sarcopenia therapy, muscular dystrophy, etc.) and in some clinical conditions (e.g., creatine synthesis defects), at much higher doses than this; yet, there have not been any safety issues regarding carcinogenesis reported by the FDA in relation to creatine supplementation. Moreover, there are reports that diets of Alaskan and Greenland natives who consume more than 95% of their diet from meat from fish, seals, and whales which would provide 6-12 grams or more of multigenerational daily creatine intake have no known increased risk of carcinogenesis related to this habitual creatine intake (Brosnan and Brosnan, 2016, Cordain et al., 2002). These dietary intakes are similar to, or higher than, recommended creatine monohydrate supplementation doses for most healthy and clinical populations.

Fourth, Zhang et al. (2021) reported that creatine supplementation provided to implanted cancer cell lines *in vivo* and *in vitro* was associated with a significant, hitherto unknown non-energy-related off-target effect by activation of the Smad2/3 signaling pathway through MPS1 (Zhang et al., 2021). This led to an increased incidence of metastasis formation and higher mortality in creatine-supplemented mice compared to controls. The authors used several human gene expression data sets from patients with primary and metastatic cancers and found a significant increase in AGAT (*GATM*) and some increase in *GAMT* with no change in *CKMT2, CKM, CKB* or *SLC6A8* mRNA. Their interpretation of these data was that the upregulation of the aforementioned mRNA expression was for increased energy supply to enhance metastasis formation. They then showed that targeting suppression of endogenous *AGAT* (*GATM*) and pharmacological inhibition of MPS1 in the cancer cell lines and animals *prevented* creatine-mediated metastasis. However, if cancer cells were to upregulate the Cr-PCr system soley for enhanced energy supply, in a manner analogous to the Warburg phenomenon, it would be expected that the other components of the system (i.e., *CKM, CKB, CKMT2* and *SLC6A8*) would also be upregulated. Given that ~ 70% of cellular S-adenosylmethionine (SAM) is diverted towards creatine synthesis at the *GAMT* level to methylate guanidinoacetate, the far more plausible role for the observed upregulation was to form creatine and S-adenosylhomocysteine (SAH) (Brosnan and Brosnan, 2016). The cancer cell utilization of this pathway, to increase the rate of purine (cysteine) synthesis *and* hypomethylated DNA for the low SAM/SAH ratio, will lead to DNA hypomethylation that is associated with chromosomal instability, aneuploid, and other factors important in malignant and metastatic transformation (Ehrlich, 2006, James et al., 2002). Creatine supplementation has been well known to suppress the expression of the first and rate-limiting enzyme for endogenous creatine synthesis (*AGAT* or *GATM*), but not *GAMT* (Walker, 1979), the provision of exogenous creatine could actually suppress this pathway and lead to hypermethylation and less DNA synthesis and attenuate tumor progression and less activation of MPS and Smad 2/3 The latter may be one of the factors that lead to the observation of Zhang (2021) and others that creatine supplementation has anti-tumor effects in the primary cells where genetic manipulation of *GATM* expression did not alter primary tumor cells and was only involved in the metastatic cells. Irrespective of the mechanism(s) involved, the data presented in the current paper further supports that even massive doses of creatine had either no effect or suppressed the primary tumor cell growh but appeared to enhance the metastatic potential in the murine model.

In addition, it has been well established that there are species-specific effects from creatine supplementation, such that findings observed in mice may not translate to other rodents or humans (Kreider et al., 2003, Tarnopolsky et al., 2003). In fact, the study by Tarnopolsky et al. (2003) found that long-term creatine supplementation in much lower doses than used by Zhang et al. (2021) resulted in liver inflammation in mice, not rats. Given that inflammation enhances the metastatic environment (Brodt, 2016, Potikha et al., 2013), it is most likely that the propensity for liver metastases to invade and/or proliferate as reported by Zhang et al. (2021) was due to a permissive niche due to murine species-specific hepatic inflammation. Furthermore, mice are prone to hepatocellular carcinoma, pituitary tumors, and lymphoma, and yet, there was a 9% median healthy survival advantage in large numbers of mice given creatine monohydrate for most of their lives at doses higher than most humans would consume (Klopstock et al., 2011) suggesting that primary tumor growth and metastases were not enhanced during the life-span of such tumorogenic murine species, in spite of life long creatine consumption at doses closer to those consumed by humans. Thus, putting all the data together, it appears that

the data from Zhang and colleagues (2021) supports the data of others that creatine supplementation even in extremely high, non-physiological doses either does not affect or actually suppresses tumor growth; however, the known species-specific effect of creatine supplementation inducing liver inflammation does lead to a permissive environment that enhances liver metastases. It is important to note that the effect of creatine upon liver inflammation seen in the murine model was not observed in rats (Tarnopolsky et al., 2003), and numerous studies in healthy men and women (Kley et al., 2013, Kreider et al., 2003, Kreider and Stout, 2021, Kreider et al., 2017), and those with a broad spectrum of clinical disorders (Tarnopolsky et al., 2004), have not shown any clinical indicators of liver inflammation/disease.

Finally, we are most concerned about how these new findings may confuse athletes, patients and other individuals consuming creatine monohydrate, discourage new clinical trials on the therapeutic effects of this nutrient, and lead to misleading recommendations by health care practitioners and authorities concerning human creatine supplementation. Zhang et al. (2021) called for caution when considering dietary creatine supplementation to improve muscle mass or treat diseases based upon a single study in a murine model using non-physiological doses of creatine monohydrate. In fact, they did not call for caution, they blatantly overstated their results and claimed that, "*Additional creatine supplement likely does not benefit recovery of the patients and instead **will** promote cancer metastasis.*" It would be equally inappropriate for people to render definitive medical claims of efficacy for drugs or nutraceuticals based upon a single or even multiple murine studies as these require human verification. In the context of there being no evidence of carcinogenesis or other significant negative health-related outcomes after many hundreds of human trials and over 30 years of real world observation, it is even more egregious that the authors make a health claim based upon a single murine study given all the caveats described above for a supplement that has a documented history of providing health benefits to many clinical populations. Given that muscle mass loss associated with cancer cachexia is a major risk factor for cancer death (Kays et al., 2020, Miyamoto et al., 2019, Pak et al., 2019), and creatine is well known to have beneficial effects in maintaining muscle mass (Chilibeck et al., 2017, Devries and Phillips, 2014), we feel this warning is highly speculative even to the cancer population, premature, and inconsistent with the overwhelming safety data on creatine monohydrate supplementation in healthy individuals and patient populations studied to date (Kreider et al., 2017, Kreider and Stout, 2021). The relevance of murine or other animal models to human physiology is questionable (Nicastro et al., 2012, Kreider, 2003, Tarnopolsky et al., 2003).
While we agree that these findings should be explored further and it may be wise as an entirely precautionary measure that individuals with confirmed cases of aggressive forms of metastasizing cancers not supplement their diet with non-physiological, or excessive amounts of creatine monohydrate (e.g., 50 - 100 grams/day), we do not agree that healthy individuals or clinical populations who may benefit from creatine monohydrate supplementation should be discouraged from taking this at recommended doses that have been found to be safe and effective. Moreover, there is no founded reason why the vast community worldwide consuming creatine in their diet or via supplements should fall into a pandemic hysteria or panic based on results of this study, whose extrapolations to humans are scientifically flawed and misleading.

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Conflicts of Interest: R.B.K. has conducted industry sponsored research on creatine, received financial support for presenting on creatine at industry sponsored scientific conferences, and has served as an expert witness on cases related to creatine. Additionally, he serves as Chair of the Scientific Advisory Board for AlzChem who sponsored a special issue on Creatine in Health and Clinical Disease for the journal Nutrients. T.W. is a scientific consultant for Crearene, a start-up company for intra-dialytic supplementation of creatine for dialysis patients. M.A.T. is the president and CEO of Exerkine Corporation/Stayabove Nutrition and the company sell 2 products that contain creatine monohydrate (CREATINE1 and MUSCLE5) and the creatine was purchased from AlzChem. He was a co-author on a Cochrane review related to the use of creatine in muscular dystrophy (Cochrane Database Syst Rev. 2013 Jun 5;2013(6):CD004760., PMID: 23740606). He received partial funding and in-kind creatine monohydrate supplements from a company (AVICENA) for previous studies looking at the potential therapeutic use of creatine in human disease and exercise performance. He received a grant from the US-MDA evaluating the use of creatine monohydrate in Duchenne muscular dystrophy (Neurology. 2004 May 25;62(10):1771-7). J.R.S. has conducted industry-sponsored research on creatine and other nutraceuticals over the past 25 years. Further, J.R.S. has also received financial support for presenting on the science of various nutraceuticals, except creatine, at industry-sponsored scientific conferences. L.Y. serves on the Scientific Advisory Board for AlzChem who sponsored a special issue on Creatine in Health and Clinical Disease for the journal Nutrients and is also an inventor on patents covering creatine for immunotherapy filed by the University of California, Los Angeles (UCLA). B.G. has received research grants, creatine donation for scientific studies, travel support for participation in scientific conferences and honorarium for speaking at lectures from AlzChem and is a member of the Scientific Advisory Board for AlzChem. R.H. does consulting work through Junipa. Ltd which is focused on creatine & beta-alanine advice. D.G.C. has conducted industry sponsored research involving creatine supplementation, received creatine donation for scientific studies and travel support for presentations involving creatine supplementation at scientific conferences. In addition, D.G.C. serves on the Scientific Advisory Board for AlzChem (a company which manufactures creatine) and has previously served as the Chief Scientific Officer for a company that sells creatine products. S.C.F. has previously served as a scientific advisor for a company that sold creatine. J.A. is the CEO of the International Society of Sports Nutrition (ISSN). The ISSN has received grants from companies that market/manufacture creatine monohydrate. He has also received funding for research on creatine monohydrate. E.S.R. has conducted industry-sponsored research on creatine and received financial support for presenting on creatine at industry-sponsored scientific conferences. Additionally, he serves as a member of the Scientific Advisory Board for AlzChem. B.W. serves on the Scientific Advisory Board for AlzChem who sponsored a special issue on Creatine in Health and Clinical Disease for the journal Nutrients. D.K. works for a contract research organization that conducts research with dietary supplements. D.K. has been involved in contract research with creatine as the ingredient of interest. In addition, D.K. reports he formerly sat on the Scientific Advisory Board of Dymatize (BellRing Brands), and that Dymatize sells creatine (board membership ended January 2021). D.K. has acted as an Expert Witness in U.S. Federal and Civil lawsuits regarding dietary supplements. None have involved creatine. D.K. reports that he is also works with a consultancy group (Metavantage Sciences, Inc.), however the group has not done any contract work for companies who sell creatine. T.N.Z. is the CEO of The Center for Applied Health Sciences, a privately held contract research organization that has received external funding from companies that do business in the dietary supplement, natural products, medical foods and functional foods and beverages industries. T.N.Z. has received grants and contracts to conduct research on dietary supplements; has served as a paid consultant for industry; has received honoraria for speaking at conferences and writing

articles about functional foods and dietary supplements; receives royalties from the sale of several sports nutrition products (none related to the product/ingredient examined in the present study); and has served as an expert witness on behalf of the plaintiff and defense in cases involving dietary supplements. T.N.Z. is also co-inventor on multiple patent applications within the field of dietary supplements, applied nutrition and bioactive compounds. M.J.O. was a former member of the Scientific Advisory Board for Dymatize Nutrition, a company that sold creatine as one of its products and published one Nutrients article with fees paid for by AlzChem. S.M.A. has received grants to evaluate the effects of dietary supplements, serves or has served on scientific advisory boards for sport nutrition companies and nutrition organizations, and has served as a consultant for supplement companies. A.R.J. has consulted with and received external funding from companies who sell certain dietary ingredients and have received remuneration from companies for delivering scientific presentations at conferences. A.R.J. has also written for online and other media outlets on topics related to exercise and nutrition. B.C. has received grants and contracts to conduct research on dietary supplements; has served as a paid consultant for industry; has received honoraria for speaking at conferences and writing articles related to dietary supplements; and has served as an expert witness on behalf of the plaintiff and defense in cases involving dietary supplements. K.M.D. is a paid member the AlzChem Scientific Advisory Board. A.S.R. conducts sponsored research on creatine and other dietary supplements and serves as a scientific advisor for AlzChem and Ladder, companies that make/use creatine. D.A.B. serves as science product manager for MTX Corporation® in Europe (a company which distributes, sells, and does research on nutritional supplements including creatine), has acted as a scientific consultant for MET-Rx and Healthy Sports in Colombia, has received honoraria for speaking about creatine at international conferences and serves as a scientific affiliate to the scientific advisory board for AlzChem. R.J. is cofounder of Increnovo, LLC which works with industry to develop evidence-based nutritional supplements A.L.A. was the co-founder of Experimental and Applied Sciences, which introduced creatine monohydrate into the North American dietary supplement market in 1993. He currently serves as President and Chief Scientific Officer of Imaginutrition, Inc., which works with industry to develop and market evidence-based consumer goods. S.M.O. serves as a member of the Scientific Advisory Board on creatine in health and medicine (AlzChem LLC). S.M.O. owns patent "Sports Supplements Based on Liquid Creatine" at European Patent Office (WO2019150323 A1), and active patent application "Synergistic Creatine" at UK Intellectual Property Office (GB2012773.4). S.M.O. has served as a speaker at Abbott Nutrition, a consultant of Allied Beverages Adriatic and IMLEK, and an advisory board member for the University of Novi Sad School of Medicine and has received research funding related to creatine from the Serbian Ministry of Education, Science, and Technological Development, Provincial Secretariat for Higher Education and Scientific Research, AlzChem GmbH, KW Pfannenschmidt GmbH, ThermoLife International LLC, and Monster Energy Company. S.M.O. is an employee of the University of Novi Sad and does not own stocks and shares in any organization. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results. C.M.K. has conducted industry sponsored research on creatine and other dietary supplements and has received financial support for presenting on various dietary ingredients at industry sponsored scientific conferences. Additionally, he is a Scientific Affiliate member of the Scientific Advisory Board for AlzChem who sponsored a special issue on Creatine in Health and Clinical Disease for the journal Nutrients. M.B. is President of NovaNeuro Srl, an academic spinoff which commercializes dietary supplements containing creatine. Other authors report no conflicts of interest.

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