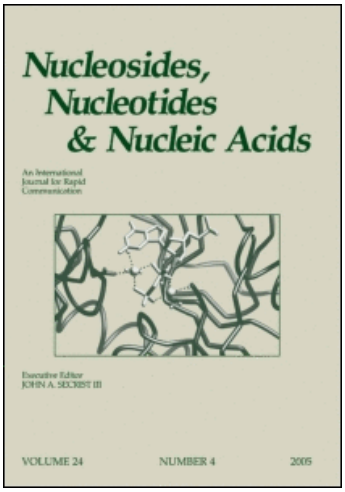

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Purine and Pyrimidine Metabolism in the Fist Decade of the 21st Century—Highlights and Perspectives

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PURINE AND PYRIMIDINE METABOLISM IN THE FIST DECADE OF THE 21ST CENTURY—HIGHLIGHTS AND PERSPECTIVES

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INTRODUCTION

The 13th International Symposium on Purine and Pyrimidine Metabolism in Man (PP09) was held in the archipelago outside Stockholm, Sweden, during the third week in June 2009. In the tradition of these symposia, the participants—150 scientists from 17 countries—represented both basic scientists in biomedical research and clinical scientists from many disciplines, with a relatively high proportion of younger participants. The history of the international symposia on purines and pyrimidines spans over almost four decades starting in Tel Aviv in 1973 with subsequent meetings every two or three years. A European Society for the Study on Purine and Pyrimidine Metabolism in Man (ESSPPMM) was founded in 1987 by the late Dr. H. Anne Simmonds, who passed away in April 2010. The ESSPPMM organized its own series of meetings, but the international symposium movement and the European society merged in 2005. The 12th International Symposium on Purine and Pyrimidine Metabolism in Man was held in Chicago, Illinois, USA, and was the first symposium organized by the newly formed Purine and Pyrimidine Society (www.PPSociety.org). The 13th Symposium in Stockholm is, thus, the second under the auspices of this society and the first symposium in Scandinavia. The history and background of these symposia are well presented in previous issues of the proceedings.[1–3]

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TABLE 1 International and European symposia on purine and pyrimidine metabolism

Year	Venue	Organizer
1973	1st International Symposium on Purine Metabolism, Tel Aviv, Israel	A. De Vries
1976	2nd International Symposium on Purine Metabolism, Vienna, Austria	M. M. Müller
1979	3rd International Symposium on Purine Metabolism, Madrid, Spain	A. Rapado
1982	4th International Symposium on Purine and Pyrimidine Metabolism, Maastricht, the Netherlands	C. H. M. M. de Bruyn
1985	5th International Symposium on Purine and Pyrimidine Metabolism, San Diego, California, USA	J. E. Seegmiller
1987	1st European Symposium on Purine and Pyrimidine Metabolism, Chateaux d'Oeux, Switzerland	F. Roch-Ramel
1988	6th International Symposium on Purine and Pyrimidine Metabolism, Hakone, Japan	K. Mikanagi
1989	2nd European Symposium on Purine and Pyrimidine Metabolism, Gut Ising, Germany	N. Zöllner
1991	7th International/3rd European Symposium on Purine and Pyrimidine Metabolism, Bournemouth, United Kingdom	H. A. Simmonds
1993	4th European Symposium on Purine and Pyrimidine Metabolism, Nijmegen, the Netherlands	R. A. de Abreu
1994	8th International Symposium on Purine and Pyrimidine Metabolism, Bloomington, Indiana, USA	M. W. Taylor
1995	5th European Symposium on Purine and Pyrimidine Metabolism, Termoli, Italy	A. Giacomello
1997	9th International/6th European Symposium on Purine and Pyrimidine Metabolism, Gmunden, Austria	M. M. Müller
1999	7th European Symposium on Purine and Pyrimidine Metabolism, Gdansk, Poland	M. Makarewicz
2000	10th International Symposium on Purine and Pyrimidine Metabolism, Tel Aviv, Israel	O. Sperling
2001	8th European Symposium on Purine and Pyrimidine Metabolism, Bruges, Belgium	G. H. van den Berghe
2003	11th International/9th European Symposium on Purine and Pyrimidine Metabolism, Egmond aan Zee, the Netherlands	G. J. Peters
2005	10th European Symposium on Purine and Pyrimidine Metabolism, Prague, Czech Republic	I. Sebesta
2007	12th International Symposium on Purine and Pyrimidine Metabolism, Chicago, Illinois, USA	M. A. Becker/R.L. Sabina
2009	13th International Symposium on Purine and Pyrimidine Metabolism, Lidingo, Stockholm, Sweden	S. Eriksson

The locations and organizers for the preceding symposia are presented in Table 1.

MISSION OF THE MEETING

The ambition of the Purine and Pyrimidine Society is to improve diagnosis, treatment, and understanding of inherited and acquired purine and

pyrimidine disorders, as well as normal purine and pyrimidine metabolism. The advances in the field should be disseminated to help to improve treatment of diseases such as cancer, cardiovascular and renal diseases, immune disorders, viral infections, inflammatory diseases, and any disease that may benefit from treatment with a purine or pyrimidine or an analogue compound. Furthermore, monitoring and adjustment of uric acid concentrations in body fluids is a field in biomedicine that has been of central interest. This is an overall ambitious task and in order to try to cover this broad area of interests in a somewhat shorter time than in previous symposia, the 13th symposium in Stockholm was organized into 10 sessions during four days. Each session consisted of presentations by two to three invited leaders in their fields as well as two to three speakers selected from the submitted abstracts. In addition, there were two poster sessions starting with short, oral presentations of selected posters; altogether, 80 posters were presented. Allocation to the sessions was performed by the Scientific Committee of the Purine and Pyrimidine Society after evaluation of all abstracts. All speakers and accepted poster authors were encouraged to submit manuscripts for evaluation and publication in this special issue of *Nucleosides, Nucleotides & Nucleic Acids*.

SCIENTIFIC SESSIONS

The topics and the chairpersons of the sessions of PP09 are presented in Table 2. The PP09 meeting highlighted several new developments in the purine and pyrimidine field, combining both classical subjects and new approaches. The establishment of the pathophysiology of hyperuremic conditions served as a starting point for the great expansion of the understanding of purine metabolism during the last decades. The use of allopurinol as xanthine oxidase inhibitor and as a drug, controlling gouty diseases, can be

TABLE 2 Sessions and chairpersons of Purine and Pyrimidine Metabolism in Man

Session	Subject	Chairs
1	Hyperuricemic diseases	M. A. Becker and J. G. Puig
2	Inflammation and autoimmune diseases	C. Peterson and A. M. Marinaki
3	Enzyme regulation	F. Bontemps and L. Thelander
4	Structure-function and drug design	V. Schramm and J. Steyaert
5	PP in malignancies, toward personal medicine	G. Juliusson and G. J. Peters
6	PP as antimicrobials including anti-viral agents	A. Karlsson and J. Balzarini
7	PP in cell cycle regulation, epigenetics, and signal transduction	W. Plunkett and B. Mitchell
8	Inborn errors and genetic variation of metabolism	R. T. Smolenski and A. B. P.Van Kuilenburg
9	PP and mitochondrial diseases	V. Bianchi and P. Reichard
10	Purine receptors and transport	B. Fredholm and M. Pastor Anglada

considered as a hallmark in development of modern chemotherapy. Therefore, it is highly satisfactory that during PP09 results were reported from a large clinical trial comparing the new xanthine oxidase inhibitor febuxostat with allupurinol with a superior performance of the former. Thus, after many years, there is an alternative drug to treat hyperurecimia. Another type of treatment of this condition is by administration of the pegylated recombinant urate oxidase enzyme, which leads to hypourecimia. Results were presented indicating that sustained hypourecimia was not associated with increased oxidative stress, which raises questions concerning the importance of urea as a free radical scavenger. The potential negative role of uric acid in other diseases such as cardiovascular and renal disease is now more and more apparent, and some progress in the establishment of reliable animal model for hyperuricemic conditions was described. The mechanism for the neurodegenerative symptoms associated with hypoxanthine-guanine phosphoribosyl transferase (HGPRT) deficiency in Lesch Nyhan disease is still not well understood, but genotype-phenotype correlations indicate that mutations predicted to cause complete enzyme deficiency are more likely to be associated with severe variants of the disease. The reason for the basal ganglia defects in patients is most likely related to the multiple roles of HGPRT in neurogenesis as revealed in human model cell culture studies with RNAi knock-down technology. Establishment of knock-out mice for xanthine oxidase, the urate transporter SLC22a12 (urat-1), helped to elucidate the importance of these enzymes in hyperuricemia.

In the last decade, there has been a boom in the field of "omics," including pharmacogenomics, proteomics, and metabolomics. Studies on purine and pyrimidine metabolism were and are by definition strong in metabolomics, making the step toward pharmacogenomics easy. It is, therefore, not surprising that pharmacogenomic profiling for purine antimetabolites (thiopurine administration) was among the first to be approved by the Federal Drug Administration (FDA). Several are likely to be followed and were discussed at the PP09 meeting.

Optimal dosing of thiopurines to either leukemia patients or inflammatory diseases such as inflammatory bowel disease (IBD) still remains a challenge. The separate steps in thiopurine metabolism, both activation and degradation, are well known. However, whether methylation should be considered as an activation process or whether it positively contributes to the efficacy of 6-mercaptourine (6MP) is still a matter of debate. Several polymorphisms of the methylating enzyme, thiopurine methyl transferase (TPMT) have been well characterized, showing an association between polymorphisms with a low TPMT activity, which were associated with severe toxicity of 6MP in childhood leukemia, due to high accumulation of thioguanine nucleotides (TGN) in lymphoid cells. However, this effect is also beneficial for elimination of cancer cells. Alternatively, although a high TPMT will prevent formation of TGN, methylated thiopurines can inhibit purine de

novo synthesis. It was discussed whether 6-thioguanine would be a better alternative for treatment of IBD, since it is a direct precursor for TGN, is poorly methylated, and has an acceptable oral bioavailability. Another target that may play an unrecognized role is methylthioadenosine phosphorylase (MTAP), which is frequently deleted in cancer cells leaving these cells completely dependent on purine de novo synthesis or hypoxanthine salvage, and more sensitive to thiopurines. Thiopurine sensitivity may also be decreased by enhanced efflux of the mononucleotides by the ABC transporters, MRP4, and MRP5. Despite the fact that various enzymes play an important role in thiopurine activity, prediction of 6MP efficacy in both IBD and leukemia is much farther advanced that for many other anti-inflammatory and anti-cancer drugs.

Increased understanding of the pathways of purine and pyrimidine metabolism in organelles, whole cells and tissues requires better molecular knowledge concerning the key regulatory enzymes and this fact was yet again clearly demonstrated during PP09. During the last 10 years a major advance in the field is the determination of the structure of many enzymes in purine and pyrimidine metabolism. A special emphasis at this meeting was on anabolism of deoxynucleosides and deoxynucleotides with overview presentations of the properties and specificities of deoxynucleoside kinases, including the mitochondrial thymidine kinases, which play key roles in mitochondrial deoxynucleotide synthesis. The broad substrate specificity of deoxycytidine kinase (dCK) was discussed in relation to its structure and function. Analysis of the active site structure in the enzyme adopting different nucleotide induced conformations, explains much of its kinetic properties. Thus, the understanding of the functional regulation of this enzyme has greatly increased but the mechanism of its tissue expression is not clear cut and it may be regulated by promotor hypermethylation and miro-RNA expression. The role of micro-RNA processing and target selection by RNA editing in regulating the phosphoribosyl pyrophosphate synthetase 1 expression in brain represented an important contribution to a new and expanding field.

Novel findings concerning the role of the ribonucleotide reductase pathway in post mitotic cells and in different mouse tissues during development were described. It was concluded that this is a cytosolic process and the large subunit R1 and the p53 inducible small subunit, p53R2, can be found in resting cells at low but significant levels to support mitochondrial and repair DNA synthesis with deoxynucleotides but to varying extent in different tissues and during different developmental periods. The complexity of the enzyme networks i.e. the combined activities of the catabolic and anabolic enzymes, that ultimately determine the steady state levels of the deoxynucleotides in different cellular compartments, has been elegantly delineated in cell culture studies with quiescent and proliferating human fibroblasts. The variable tissue specific expression and post transcriptional regulation of

the mitochondrial thymidine kinase 2 (TK2) enzyme have recently been clarified. Apparently the levels of active TK2 in relation to the ribonucleotide reductase pathway are a key factor for the tissue specific pattern of symptoms in several forms of the mitochondrial DNA depletion syndrome. This information provides vital clues to the understanding of inborn errors of metabolism and the variation in efficacy and toxicity associated with nucleoside analog therapy. The latter should also be seen in view of the role of deoxynucleotide supply in repair of DNA damage caused by various nucleoside analogs. Most analogs act by incorporation into DNA or they prevent incorporation of the natural deoxynucleotide into DNA. The difference between these analogues is manifold, for example, the extent by which they incorporate plays a role, as well as the DNA polymerase, and whether this causes chain termination or masked chain termination. For repair, the right enzyme should be present as well as a sufficient concentration of deoxynucleotides, produced either by de novo synthesis catalyzed by ribonucleotide reductase or via salvage enzymes such as deoxycytidine and thymidine kinases, providing the deoxynucleotides needed. In various presentations these aspects were treated separately, taken together they demonstrate the importance of this process.

The vastly increased knowledge concerning enzyme structure and function acquired during the last decade is now in the process of being translated into drug design efforts both in the industry and academia. The concept of structure based drug design is gradually gaining real substance and urgency since so-called hypothesis neutral high through-put screening efforts have in many cases given minimal returns. There were several excellent examples presented at PP09 of hypothesis driven drug design projects based on transition state analog studies and large scale structural determinations. New modes of leaving group activation in nucleoside hydrolases have been delineated and the results may be relevant to many chemical transformations of aromatic compounds as well as RNA-catalyzed reactions. New three-dimensional structures of about 25 proteins in human nucleotide metabolism have been determined in the Swedish division of the Structural Genomic Consortium and new regulatory interactions of purine and pyrimidine intermediates will be investigated in a form of "in vitro metabolome" screen. The most powerful inhibitors of purine nucleoside phosphorylases have been synthesized based on transition state analysis of intrinsic kinetic isotope effects. These findings, which are based on experimental and computational chemistry-biochemistry, have during the last years been translated into clinically very promising anti-cancer and potential anti-microbial agents. This work represents one of the best examples of the power of applying basic molecular science to produce new chemical compounds that can cure severe diseases. These results should hopefully motivate generous future support for basic research as the foundation for advancement in biomedicine.

Development of novel approaches towards personalized treatment with anticancer drugs is a booming field. A number of new antimetabolites have

been developed in the last decades and brought into the clinic, being highly successful in treatment of various tumors. For instance, gemcitabine is part of standard therapy for various malignancies, such as pancreatic cancer and non-small cell lung cancer (NSCLC). Its efficacy is dependent on cellular uptake by the equilibrative (ENT) and concentrative nucleoside transporters (CNT), subsequent activation by dCK and inhibition of its target ribonucleotide reductase. Systemic degradation by cytidine deaminase (CDA) is a major limiting factor. A high CDA activity is associated with certain SNPs, leads to decreased toxicity and efficacy; however, a much better efficacy is observed at lower CDA activities with more but acceptable toxicity. Apparently, patients with a high CDA level seem to be under-treated when given the standard dose.

The various presentations on different transporters demonstrated that the importance of both influx and efflux transporters has been underestimated in the past for the efficacy of nucleoside analogs in various diseases and should be taken into account in future drug development. This challenge led to the design of drugs to bypass transport, for example, since a low expression of ENT was associated with a poor response to gemcitabine in pancreatic cancer, transport independent uptake of the drug would be beneficial. This was achieved by attachment of a lipophilic chain to the 5′-position of gemcitabine, which yields a drug independent of the uptake mechanism. This led to prolonged accumulation in cancer cells both with normal but also ENT depleted cells, and even oral application could be feasible. Similarly, capecitabine, a prodrug of 5-fluorouracil (5FU) has a high oral bioavailability due to the presence of a lipophilic chain at the N-4 amino group. Its activation is dependent on deamination by CDA, while conversion of the intermediate 5′-deoxy-5-fluorouridine (5′DFUR) to 5FU was initially considered to be solely dependent on thymidine phosphorylase (TP), but induction of uridine phosphorylase (UP) markedly enhanced sensitivity to 5′DFUR as well. Human tumors contain a high expression of both UP and TP, which will lead to specific activation of the drug in the tumor.

Next to the pyrimidine analogs, several purine antimetabolites have promising activity not only against leukemia, but also against solid tumors; one such example is chloro-adenosine, which interferes both with RNA and DNA synthesis. A deficiency of the above-mentioned MTAP, which is associated with increased sensitivity to thiopurines, may also play a role in the efficacy of pemetrexed (PMX), an anti-folate thymidylate synthase (TS) inhibitor, which can inhibit purine de novo synthesis. PMX is widely used for treatment of non-squamous NSCLC and malignant mesothelioma, which have a high degree of MTAP deficiency, and which may be an additional marker for PMX sensitivity.

Anti-viral nucleoside/nucleotide analogs are among the most valuable drugs presently on the market and this field has grown dramatically with many regular large meetings devoted to the discovery, development and

use of these drugs. There were several presentations during PP09 where new drug targets were identified and ways described to circumvent their need for cellular enzymes to convert nucleosides to their active nucleotide metabolites. The poxviruses are a group of large cytoplasmic viruses that can cause diseases in humans and animals and at present new efficient anti viral treatments are available. The reaction converting thymidylate to thymidine diphosphate is a unique reaction, which is required both for the salvage and de novo synthesis of dTTP. The enzyme responsible for this reaction thymidylate kinase is considered an excellent drug target but so far no clinically useful inhibitors are known. New results concerning the structure of *Vaccinia* virus thymidylate kinase demonstrated that this enzyme shows a different subunit organization and active site geometry compared to the human enzyme. Therefore, bulkier nucleotide analogs could bind, which opens an avenue for rational drug design. The design, synthesis and surprising new activities of phosphoramidate analogs of well-known antiviral nucleosides were revealed and, for example, the anti-herpes nucleoside bromovinyl deoxyuridine is in the ProTide form active as an anticancer compound.

In contrast to the general use of nucleosides and nucleotides as antiviral agents there are no such analogs, that serve as antibacterial drugs. However, the knowledge about purine and pyrimidine metabolism in various pathogenic bacterial strains and protozoa has increased dramatically in recent years and the occurrence and properties of deoxyribonucleoside salvage enzymes in Gram-positive and Gram-negative bacteria was reviewed. New unique specificities were revealed and the possibilities to use these variant enzymes also in gene therapy and for synthetic purpose were described. Two important targets for drug development against parasitic protozoa have been identified and recent results concerning the dUTPase from *Trypanosoma brucei* and *Plasmodium falciparum* indicate that this enzyme is found in different forms and has an essential role in parasite proliferation. Trypansoma adenosine kinase and MTAP were found to be key enzymes for the growth inhibitory effect of deoxyadenosine and non-cleavable analogs such as AraA could potentially be developed into anti-trypanosoma agents.

In the last decade increasing evidence demonstrates that epigenetic regulation plays a key role in gene expression. Many genes have CpG islands in their promoters, which are targets for methylation, generally leading to decreased expression of the gene and protein. Several important DNA repair enzymes have a low expression due to a high methylation content, which will reduce the efficacy of drugs such as temozolomide and cisplatin. Treatment with hypomethylating agents which inhibit DNA methyltransferase (DNMT) such as aza-cytidine, aza-deoxycytidine or zebularin, can enhance the efficacy of these drugs. At the posttranslational level proteasomal degradation of the enzyme plays a role and may affect the efficacy of IMP-dehydrogenase inhibitors, either directly or via nucleostemin whose degradation can be prevented by proteasome inhibitors. Alternatively, nutlin, a p53-mdm2

inhibitor may also prevent degradation of nucleostemin. Nutlin is also a cell cycle regulator. Specific inhibition of cell cycle dependent kinases (cdk) or checkpoint kinases (e.g., chk1) plays an important role in DNA repair of DNA targeted drugs such as sapacitabine (CNDAC), which causes cells to accumulate in the G2M phase.

Although TP plays a role in both drug activation and inactivation, it has various other roles in disease. A high expression in tumors or tumor-associated stromal cells is associated with an increased invasion and migration of tumor endothelial cells, possibly through an accumulation of thymidine derived sugars, which enter the anaerobic glycolysis and the pentose phosphate shunt. On the other hand, a deficiency of TP is associated with MNGIE (mitochondrial neurogastrointestinal encephalomyopathy). This deficiency will affect mitochondrial energy metabolism and results in accumulation of thymidine and thymidine nucleotides, which inhibit mitochondrial DNA synthesis and ATP production. These effects may be due to an imbalance in mitochondrial deoxynucleotide pools. Several inborn errors proved to be excellent model systems to study the role of these enzymes in cancer and drug metabolism. For instance, deficiency or decreased activity of dihydropyrimidine dehydrogenase (DPD) can lead to neurological effects in children, although many do not show symptoms. However, a low DPD activity in cancer patients treated with 5-fluorouracil at an adult age may lead to lethal toxicity. The DPD gene is very large and many genetic aberrations have been identified. Unfortunately, this has not led to a very clear association of one aberration with DPD deficiency.

Many normal nucleosides and nucleotides play a role in cellular signalling, controlling various processes in the cell such as proliferation, DNA repair, angiogenesis, and neuronal activation. These include the cyclic nucleotides, adenosine, and uridine. However, also nucleotides such as ATP play a role in cellular signalling either directly or via several membrane receptors. The study of such effects is often hampered by rapid metabolism of e.g. ATP to adenosine, so that confusion arises whether the effect of ATP is mediated directly or by one of the adenosine receptors. Much more insight

TABLE 3 Recipients of the Purine and Pyrimidine Metabolism in Man poster awards

Recipient	Institute	Title
Emeline de Viron	De Duve Institute (UCL), Brussels, Belgium	Impaired up-regulation of polo-like kinase 2 (PLK2) in B-cell chronic lymphocytic leukemia (B-CLL) lymphocytes resistant to fludarabine and 2-chlorodeoxyadenosine (CdA): A potential marker of defective damage response
Alice Preumont	De Duve Institute (UCL), Brussels, Belgium	Identification of a specific human pseudouridine 5′-phosphatase
Rosa J. Torres	La Paz Hospital, Madrid, Spain	Methylation status of HPRT1 promoter in HPRT deficiency with normal coding region

TABLE 4 Supporters of the 13th International Symposium on Purine and Pyrimidine Metabolism in Man

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in these processes was gained by inclusion of detailed metabolic studies in cellular signalling studies, not only for natural nucleosides but also analogs such as chloro-adenosine. The meeting was an excellent forum for exchange of these perspectives between classical receptor scientists and enzymologists.

Many interesting posters were presented in the poster sessions and their general message is included in this review. Three poster presenters received a prize for best posters (see Table 3).

These proceedings are the fourth in a new tradition of publication of the presentations of the Purine and Pyrimidine Meetings in *Nucleosides, Nucleotides & Nucleic Acids*, which started with the 2003 meeting, followed by those in 2005 and 2007. This has now led to an agreement between the Purine and Pyrimidine Society and Taylor & Francis, the publisher of *Nucleosides, Nucleotides & Nucleic Acids*, in which the journal will now serve as the society's official journal. In order to complete the publication process in time, we appreciate the contributions of all reviewers of the abstracts and congress proceedings. Without their help it would have been impossible to maintain a high scientific standard.

CONCLUDING REMARKS

The 2009 meeting of the Purine and Pyrimidine Society was the second meeting after merging the International and European meetings. The meeting successfully followed the paths of the original European society in its aims to study the pathophysiology of inborn errors in man and translate the insights gathered in these diseases and model systems for other applications, such as to design new modes for treatment of cancer and inflammatory diseases. The meeting was an excellent forum for multidisciplinary scientists, giving young scientists the opportunity to learn from various fields and translate the findings between the various disciplines.

Finally, the 13th International Symposium on Purine and Pyrimidine Metabolism in Man would not have been possible without the hard work of many individuals, particularly the members of the board of Purine and Pyrimidine Society as well as the co-organizers, Gunnar Juliusson, Anna Karlsson, and Curt Petersson. Furthermore, the names of the sponsors of this symposium are listed in Table 4 and we thank them for their generous support.

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