

## Metadichol® and Red Cell Distribution Width (RDW) in CKD patients

**Raghavan PR**

Nanorx Inc., New York, USA

**Abstract**

Red blood cells originate in the bone marrow. Red cell distribution width (RDW) show sizes of circulating erythrocytes (RBC) and has been explored in several large clinical databases to be a robust marker of adverse clinical outcomes in patients. The prognostic value of RDW is seen in other conditions with end-organ dysfunction such as renal failure or. Elevated RDW levels are of significance in diseases such as kidney diseases. The high RDW levels are an indication of increased oxidative stress and closely related to the presence and poor prognosis of the disease.

No known therapy exists that can normalize RDW levels. In this paper, we present here case studies using Metadichol® [1] that leads to normal RDW levels in patients with CKD and PKD.

**Keywords:** Red Cell Distribution Width; RDW; Metadichol; Bone marrow; Hematopoietic stem cells; Red blood cell; Erythropoietin; EPO; CKD; Peritoneal dialysis; Hemodialysis; EPO; TNF-alpha; Vitamin D; VDR; Inverse/protean agonist; Creatinine; eGFR; Iron and Iron saturation

### Introduction

In the 21st-century Chronic Kidney Disease (CKD) is becoming a worldwide health issue [2]. RDW elevation is seen in patients with CKD [3], Peritoneal Dialysis (PD) or Hemodialysis [4] which is a standard therapy for patients reaching End-Stage Renal Disease (ESRD). RDW has potential use as a biomarker in estimating the risk of mortality. A higher RDW is an independent risk factor for overall and CVD-related mortality in patients undergoing dialysis, and that its value was superior to others biomarkers of anaemia [5].

Although mechanisms are unknown, evidence suggests an independent relationship between RDW and clinical outcomes in many human diseases [6]. A high RDW Level indicates heterogeneity in RBC size (anisocytosis). Also, accelerating RBC destruction and ineffective erythropoiesis, are common in patients undergoing dialysis, and bone marrow dysfunction which leads to a high RDW level.

Bone marrow-derived mesenchymal stem cells have been reported to play a crucial role in the restoration of many injured vital organs [7]. Thus, hematopoiesis in dialysis patients leads to mortality associated with a high RDW.

Inflammation, which is prevalent in CKD patients, has been closely linked to RDW in many patient populations. Pro-inflammatory cytokines like TNF-alpha are well known to inhibit, induced RBC maturation and proliferation [8].

Malnutrition and protein-energy wasting, which is common in dialysis patients, increases RDW and is inversely related to nutritional index in a broad range of medical conditions [9].

The residual renal function was greater in the low RDW group than that in the high RDW group. The residual renal function has a beneficial effect on patient survival [10].

High RDW levels are associated with an increased risk of adverse outcomes in the general population and in patients with severe sepsis, heart failure, coronary artery disease, stroke, and acute kidney injury that required renal replacement therapy and kidney transplant [11].

High level of RDW impairs iron metabolism, and the resulting inflammation disrupts the process of erythropoiesis [12].

Cytokines are released when there is inflammatory stress and can inhibit erythrocyte maturation. These cytokines like TNF-alpha block the activity of erythropoietin inhibit erythrocyte maturation, and this results in the production of ineffective red blood cells and elevated RDW [13].

Given the importance of RDW in mitigating disease outcomes [14], there is only one reported study by Fici et al. [15] that evaluated the effects of nebivolol and metoprolol on RDW in hypertensive patients (Table1). Nebivolol decreased RDW marginally by about 4%. There are no known drugs available to treat this dysfunction today.

Metadichol (16 ), as we have shown earlier, binds to VDR and is also a TNF-alpha (1) inhibitor and also demonstrated that it increased platelets in Dengue patients [16]. Platelets result from hematopoietic stem cells which also is the pathway to normal erythropoiesis and normal RDW. We treated three patients with CKD and high RDW levels using Metadichol. In addition to improvement in RDW, other improvements in Creatinine, Iron, PTH is seen and a feeling of well-being [17].

### Case Presentation 1

70 years old male has been on Hemodialysis 3 days a week for five years. Treated with Metadichol at 10 mg per day. The patient is also on statins, phosphate binders and Vitamin D. He reports improved energy

RDW	Nebivolol (n=37)	Metoprolol (n=35)	P*
Before	15.75 ± 1.49	15.68 ± 1.60	0.85
After	15.07 ± 1.26	15.62 ± 1.59	0.11
P†	<0.001	0.35	

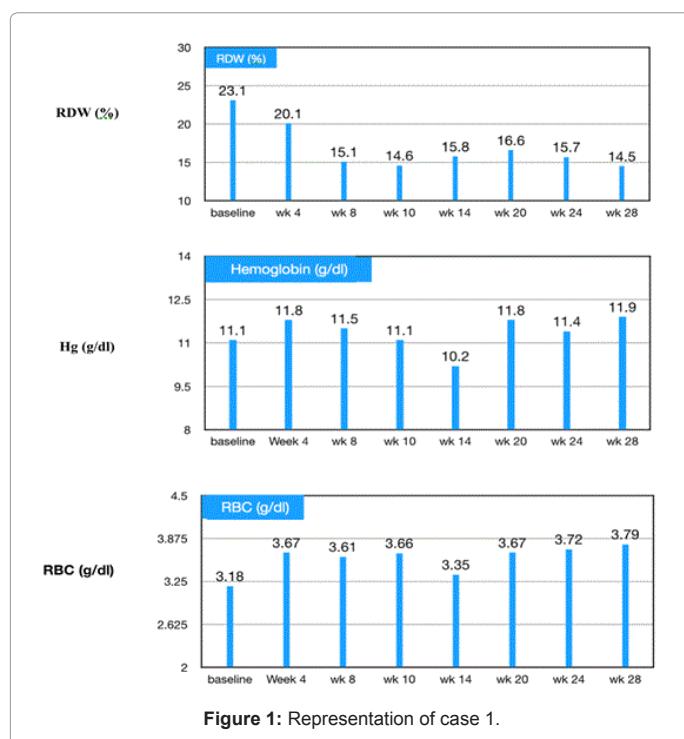
Table 1: Effects of nebivolol and metoprolol on RDW in hypertensive patients.

\*Corresponding author: Raghavan PR, Nanorx Inc., PO Box 131, Chappaqua, NY 10514, USA

Received June 27, 2017; Accepted June 30, 2017; Published July 06, 2017

Citation: Raghavan PR (2017) Metadichol® and Red Cell Distribution Width (RDW) in CKD patients. J Stem Cell Res Ther 7: 392. doi: 10.4172/2157-7633.1000392

Copyright: © 2017 Raghavan PR. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.



**Figure 1:** Representation of case 1.

and no sudden drops in pressure during dialysis (Figure 1).

### Case Presentation 2

62 years old male patient with CKD for four years. He is obese, diabetic and hypertensive and has been on hemodialysis three days a week. Treated with Metadichol® 10 mg per day. The patient was on hypertension drugs, insulin and metformin. Also, he had an accumulation of water retention in legs and was on diuretics as well. The patient lost 22 lb after starting with Metadichol®, his swelling is gone, and blood sugar has normalized. He is off insulin and metformin but still on hypertension drugs (Figure 2).

### Case Presentation 3

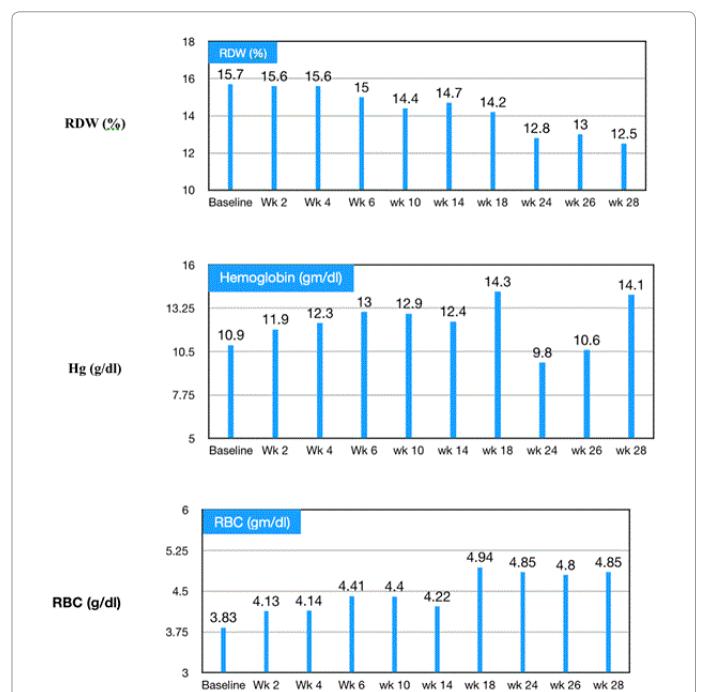
A 65 years old female patient diagnosed with Polycystic Kidney disease on dialysis for seven years before she had a kidney transplant. Undergoes infusion once a month for anti-rejection therapy but is not on dialysis. A year after the transplant she still did not feel completely normal. She had a lot of water retention and weight increase. After using Metadichol® at 5 mg per day, she feels much improved and energetic. She also lost 15 lb in weight, mostly water, and is feeling very energetic (Figure 3).

### Discussion

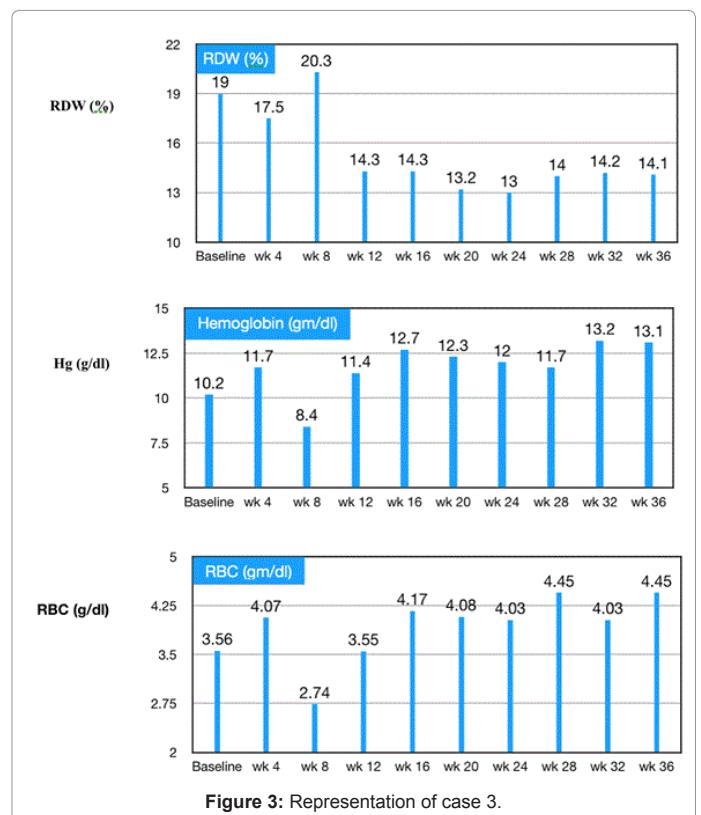
The results show that all three patients have experienced a decrease in their RDW. Also, all of them showed improvement in RBC and Hemoglobin levels. Statistical Analysis of Variance one way was carried out using JMP software from SAS showed that the following RBC were significant at  $p = 0.0023$ , but Hemoglobin was not significant with a  $p = 0.21$ .

Case 1 patient's Hemoglobin and RBC are heading in the direction of normality though at a slower pace compared to the other two cases presented. Also improvements in other parameters such as Creatinine, Iron, and Iron saturation, and loss of weight and increased energy as

well as a general feeling of wellness. All the three patients have shown improvements in various biomarkers like Creatinine, PTH, and ferritin and will be reported in due course. No adverse side effects have since Metadichol® is a natural food-based product that is completely safe (18-20).



**Figure 2:** Representation of case 2.



**Figure 3:** Representation of case 3.

Inflammation induced by cytokines like TNF-alpha, IL-1B, IL-6, etc. can have a suppressing effect on Erythropoietin (EPO) thus erythrocyte maturation, leading to the production of ineffective red blood cells and elevated RDW hemoglobin synthesis and cause chronic inflammatory anemia (21). Thus a simple explanation of the mechanism of action of Metadichol® that as a TNF-alpha inhibitor [1] it could reduce inflammatory cytokines and bring about the normalization of RDW, RBC, and HGB levels.

Previous studies have shown that Tumor Necrosis Factor alpha (TNF-alpha) as a therapeutic target in many human immune disorders, including inflammatory diseases, ischemia-reperfusion injury as well as trauma (22)]. Also, it might play an essential role in rapid necrotic regression of certain forms of tumors [23]. Therefore, it is crucial to understand the potential mechanisms that involved in the regulation of TNF-alpha in normal and disease-related cells. Recent observation indicated that histone methyltransferase G9a and heterochromatin-associated protein HP1 is essential for the silencing of TNF-alpha [24]. Epigenetically, G9a functions as the H3K9me1/2 writer whereas HP1 binds and maintains H3K9me3 at heterochromatin loci [25] suggesting that methylation of histone H3 lysine nine residues is critical for the regulation of TNF-alpha. Additionally, as G9a also interacts with DNA methyltransferase (DNMTs) and maintains DNA methylation at particular loci [26] the presence of DNA methylation might also affect the expression of TNF-alpha. Taken together, investigation of the H3K9me, as well as the DNA methylation patterns, might create a new direction for revealing the mechanisms that involved in the regulation of TNF-alpha.

Another explanation is the role of Vitamin D in the hematopoietic process. Suppression of erythropoiesis occurs in bone marrow by inflammatory cytokine due to blockage of erythroid progenitor cell proliferation and pro-erythroblast maturation. The inflammatory cytokine modulation on bone marrow erythroid progenitors desensitizes the cells to EPO, which blocks its anti-apoptotic and pro-maturation effects (27-28).

Vitamin D range of biological effects involve not just calcium and Phosphorus homeostasis, but it is also an immune modulator. This property allows it to modulate dysfunctional hematopoietic and this can affect in hematologic disorders. (29-30). Immune cells express Vitamin D receptor (VDR) which are well known to modulate innate and adaptive immunity. VDR activation can inhibit production of inflammatory cytokines up-regulates interleukin-10 (IL-10) exerting both anti-inflammatory activity and proliferative effects on erythroid progenitors. In CKD patients, vitamin D deficiency stimulates immune cells within the bone marrow to produce cytokines, leading to dysfunctional erythropoiesis. Kiss et.al. have shown that there is an inverse association between vitamin D levels and EPO CKD patients [25]. Vitamin D supplementation and Paricalcitol therapy have been shown to lead to improvement in biomarkers of inflammation (31-33).

Metadichol is a TNF-alpha inhibitor and also it binds to VDR, and hence it could be working through more than one pathway in modulating RDW and normalizing RBC and Hemoglobin levels. We have previously shown how Metadichol works on other diseases through the Vitamin D receptor as an inverse/protean agonist and other nuclear receptors (34-42). The results of this study demonstrate that Metadichol is safe and effective as evidenced by the improvement of various biomarkers such as RDW that lead to improved RBC and Hemoglobin levels in CKD patients. Metadichol has the potential to be an anti-inflammatory molecule with a broad spectrum of activity. Its constituents (long-chain lipid alcohols) are present in foods commonly

consumed on a daily basis and with no toxicity seen even with doses of up to 5000 mg/kg (18-20). Metadichol could be used as a nutritional supplement in renal and hematological diseases as a cheaper alternative. It can prevent complications from existing therapies that add to health care costs.

## References

1. Raghavan PR. US Patents 8,722,093 (2014), 9,034,383 (2015), 9,006,292 (2015).
2. Glasscock RJ, Warnock DG, Delanaye P (2017) The global burden of chronic kidney disease: estimates, variability, and pitfalls. *Nat Rev Nephrol* 13: 104-114. [\[PubMed\]](#)
3. Solak Y, Yilmaz MI, Saglam M, Caglar K, Verim S, et al. (2014) Red cell distribution width is independently related to endothelial dysfunction in patients with chronic kidney disease. *Am J Med Sci* 347: 118-124. [\[PubMed\]](#)
4. The National Forum of ESRD Networks.
5. Allen LA, Felker GM, Mehra MR, Chiong JR, Dunlap SH, et al. (2010) Validation and Potential Mechanisms of Red Cell DistributionWidth as a Prognostic Marker in Heart Failure. *J Card Fail* Vol 16: 230-238. [\[PubMed\]](#)
6. Salvagno GL, Sanchis-Gomar F, Picanza A, Lippi G (2015) Red blood cell distribution width: A simple parameter with multiple clinical applications. *Crit Rev Clin Lab Sci.* 52: 86-105. [\[PubMed\]](#)
7. Li M, Ikehara S (2013) Bone-marrow-derived mesenchymal stem cells for organ repair. *Stem Cells Int* 2013: 132642. [\[PubMed\]](#)
8. Macdougall IC, Cooper AC (2002) Erythropoietin resistance: the role of inflammation and pro-inflammatory cytokines. *Nephrol Dial Transplant* 17: 39-43. [\[PubMed\]](#)
9. Forhecz Z, Gombos T, Borgulya G, Pozsonyi Z, Prohászka Z, et al. (2009) Red cell distribution width in heart failure: Prediction of clinical events and relationship of with markers of ineffective erythropoiesis, inflammation, renal function, and nutritional state. *Am Heart J* 158: 659-666. [\[PubMed\]](#)
10. Wang AY, Sea MM, Ho ZS, Lui SF, Li PK, et al. (2005) Evaluation of handgrip strength as a nutritional marker and prognostic indicator in peritoneal dialysis patients. *Am J Clin Nutr* 81: 79-86. [\[PubMed\]](#)
11. Sun OI, Chung BH, Yoon HJ, Kim JH, Choi BS, et al. (2016) Clinical significance of red blood cell distribution width in the prediction of mortality in patients on peritoneal dialysis. *In Kidney Res Clin Pract* 35, 114-118. [\[PubMed\]](#)
12. Chiari MM, Bagnoli R, De Luca PD, Monti M, Rampoldi E, et al. (1995) Influence of acute inflammation on iron and nutritional status Indexes in older inpatients. *J Am Geriatr Soc* 43: 767-771. [\[PubMed\]](#)
13. Pierce CN, Larson DF (2005) Inflammatory cytokine inhibition of erythropoiesis in patients implanted with a mechanical circulatory assist device. *Perfusion* 20:8i-90. [\[PubMed\]](#)
14. Bujak K, Wasilewski J, Osadnik T, Jonczyk S, Kołodziejska A, et al. (2015) The Prognostic Role of Red Blood Cell Distribution Width in Coronary Artery Disease, A Review of the Pathophysiology. *Disease Markers* 2015: 824624.
15. Fici F, Celik T, Balta S, Ilyisoy A, Unlu M, et al. (2013) Comparative Effects of Nebivolol and Metoprolol on Red Cell Distribution Width and Neutrophil/Lymphocyte Ratio in Patients With Newly Diagnosed Essential Hypertension. *J Cardiovasc Pharmacol* 62: 388-393. [\[PubMed\]](#)
16. Raghavan PR (2016) Inhibition of Dengue and other enveloped viruses by Metadichol®, a Novel Nanoemulsion Lipid. *JSCHO* 8: 19-25.
17. Raghavan PR, unpublished results of the ongoing study.
18. Alemán CL, Más R, Hernández C, Rodeiro I, Cerejido E, et al. (1994) A 12-month study of policosanol oral toxicity in Sprague Dawley rats. *Toxicol Lett* 70: 77-87. [\[PubMed\]](#)
19. Alemán, CL, Más Ferreiro R, Noa Puig M, Rodeiro Guerra I, Hernández Ortega C, et al. Carcinogenicity of policosanol in Sprague-Dawley rats: A 24-month study. *Teratog Carcinog Mutagen* 14: 239-249; [\[PubMed\]](#)
20. Aleman, CL, Puig MN, Elías EC, Ortega CH, Guerra IR, et al. Carcinogenicity of policosanol in mice: An 18-month study. *Food Chem Toxicol*: 1995; 33: 573-578. [\[PubMed\]](#)

21. Cetian M, Kocaman SA, Bostan M, Çanga A, Çiçek Y, et al. (2012) Red Blood Cell Distribution Width (RDW) and its Association with Coronary Atherosclerotic Burden in Patients with Stable Angina Pectoris. *Eur J Gen Med* 9: 7-13.
22. Esposito E, Cuzzocrea S (2009) TNF-alpha as a therapeutic target in inflammatory diseases, ischemia-reperfusion injury, and trauma. *Curr Med Chem* 16: 3152-3167. [\[PubMed\]](#)
23. Idriss HT, Naismith JH (2000) TNF-alpha and the TNF receptor superfamily: structure-function relationship(s). *Microsc Res Tech* 50: 184-195. [\[PubMed\]](#)
24. El Gazzar M, Yoza BK, Chen X, Hu J, Hawkins GA, et al. (2008) G9a and HP1 couple histone and DNA methylation to TNFalpha transcription silencing during endotoxin. *J Biol Chem* 283: 32198-32208. [\[PubMed\]](#)
25. Shinkai Y, Tachibana M (2011) H3K9, methyl-transferase G9a, and the related molecule GLP. *Genes Dev* 25: 781-788. [\[PubMed\]](#)
26. Muramatsu D, Kimura H, Kotoshiba K, Tachibana M, Shinkai Y, et al. (2016) Pericentric H3K9me3 Formation by HP1 Interaction-defective Histone Methyltransferase Suv39h1. *Cell Struct Funct* 41: 145-152. [\[PubMed\]](#)
27. Zhang T, Termanis A, Özkan B, Bao XX, Culley J, et al. (2016) G9a/GLP Complex Maintains Imprinted DNA Methylation in Embryonic Stem Cells. *Cell Reports* 15: 77-85. [\[PubMed\]](#)
28. Hellwig-Burgel T, Rutkowski K, Metzen E, Fandrey J, Jelkmann W (1999) Interleukin-1 beta and tumor necrosis factor-alpha stimulate DNA binding of hypoxia inducible factor-1. *Blood* 94: 1561-1567. [\[PubMed\]](#)
29. Lacombe C, Mayeux P (1999) The Molecular biology of erythropoietin. *Nephrol Dial Transplant* 14: 22-28. [\[PubMed\]](#)
30. Macdougall IC, Cooper A (2012) The inflammatory response and Epoetin sensitivity. *Nephrol Dial Transplant* 17: 48-52. [\[PubMed\]](#)
31. Hall AC, Juckett MB (2013) The Role of Vitamin D in Hematologic Disease and Stem Cell Transplantation. *Nutrients* 5: 2206-2221. [\[PubMed\]](#)
32. Kiss Z, Ambrus C, Almasi C, Berta K, Deak G, et al. (2011) Serum 25(OH)-cholecalciferol concentration is associated with hemoglobin level and erythropoietin resistance in patients on maintenance hemodialysis. *Nephron Clin Pract* 117: c373-c378. [\[PubMed\]](#)
33. Alborzi P, Patel NA, Peterson C, Bills JE, Bekele DM, et al. (2008) Paricalcitol reduces albuminuria and inflammation in chronic kidney disease: a randomized, double-blind pilot trial. *Hypertension* 52: 249-255. [\[PubMed\]](#)
34. Raghavan PR (2017) Rheumatoid Arthritis and Osteoporosis: A Case Study. *J Arthritis* 6: 240.
35. Raghavan PR (2017) Systolic, and Diastolic BP Control in Metabolic Syndrome Patients with Metadichol® A Novel Nano Emulsion Lipid. *J Cardiol & Cardiovasc Ther* 5: 555660.
36. Raghavan PR (2017) Metadichol® A Novel Nano Lipid; GPR 120 Agonist. *Int J Diabetes Complications* 1-3
37. Raghavan PR (2017) Metadichol® and MRSA Infections: A Case Report. *J Infect Dis Ther* 5: 100317.
38. Raghavan PR (2017) Improving Longevity with Metadichol® by inhibiting Bcat-1 Gene. *J Aging Sci* 5: 1.
39. Raghavan PR (2016) In vitro Inhibition of Zika Virus by Metadichol®. A Novel Nano Emulsion Lipid. *J Immunol Tech Infect Dis* 5: 4.
40. Raghavan PR (2016) Inhibition of Dengue and other enveloped viruses by Metadichol®, a Novel Nanoemulsion Lipid. *Journal of the Science of Healing Outcomes* 8: 19-25.
41. Raghavan PR (2016) Metadichol and Type 2 Diabetes A case report. *J Sci Healing Outcomes* 8: 5-10.
42. Raghavan PR (2010) Case Report of Type1. Diabetes. *Journal of the Science of Healing Outcomes* 2: 8-9.

## OMICS International: Open Access Publication Benefits & Features

### Unique features:

- Increased global visibility of articles through worldwide distribution and indexing
- Showcasing recent research output in a timely and updated manner
- Special issues on the current trends of scientific research

### Special features:

- 700+ Open Access Journals
- 50,000+ editorial team
- Rapid review process
- Quality and quick editorial, review and publication processing
- Indexing at major indexing services
- Sharing Option: Social Networking Enabled
- Authors, Reviewers and Editors rewarded with online Scientific Credits
- Better discount for your subsequent articles

Submit your manuscript at: <http://www.omicsonline.org/submit>