THE BIOMED SCIENTIST

Newsletter of The Association of African Biomedical Scientists, Inc.

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The Association of African Biomedical Scientists, Inc. (AABS) is a not-for-profit organization whose membership is open to those who share the following goals: 1) Foster the development of Science in Africa; 2) Promote career development opportunities for Biomedical Scientists in North America; 3) Provide opportunities for young developing scientists; and 3) Encourage research collaboration in pursuit of advancing scientific knowledge.

EDITOR'S CORNER

Welcome to another issue of The BioMed Scientist, our official newsletter. I hope that you enjoy reading it. Please send your comments, suggestions or criticisms to the editor. We invite articles that are in the spirit of our goals for the next issue. Brief discussions and articles of scientific nature are welcome.

Let us utilize this forum to network and to establish relationships that enable us help one another succeed in our professional endeavors.

Editor: *Momoh Yakubu, Ph.D.*
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MESSAGE FROM THE PRESIDENT

Vincent K. Tsiagbe, Ph.D.

Fellow members of AABS: We have made progress into the fourth volume of the Biomed Scientist, and it gives me great pleasure to reflect on our achievements.

As a follow-up to the successful Satellite meeting of AABS, held in Washington, in 2007, the Board of Trustees of AABS deliberated on matters discussed, and took appropriate steps toward enhancing the stand of AABS. To this end, the Board set up a new committee named "Membership and Fundraising Committee". This committee was charged to explore avenues geared towards attracting new members, including members from Africa. This committee was also charged with the mission of defining sources of funding and seeking financial support to enable AABS hold workshops on periodic basis in African countries, on rotating basis.

A fact that is well acknowledged is that the building of robust scientific institutions cannot be done is a day. Progress has to be made in stages, however modest they might be. A case in point is "the African Science Academy Development Initiative" (ASADI), which was set up with the assumption that both scientists and nations are bound to benefit from the existence of strong, respectable, and modestly independent institutions that can effectively voice the interests of science. Even though some progress has been made since ASADI got instituted in 2004, much needs to be done. The importance of getting scientific minds together in Associations such as AABS, would be expected to provide some "grease" to ease the rough journey. It is, therefore, with great joy that we have seen a steady increase in new membership from the African continent. To make this easier the Board of Trustees voted to put in place reduced membership fees for members from Africa.

Our membership is steadily rising. However, in view of periodic relocations of members and changes in e-mail addresses, we have seen a steady rise in bounced list server mails. Members are therefore encouraged to send updated e-mail addresses to the webmaster.

Dues payments have not been at par with our enlisted membership. In order for us to face squarely the tasks that we have set forth for ourselves, members are encouraged to pay their dues on time.

We should utilize the Biomed Scientist (the official news letter of AABS), to get our voices heard on issues pertinent to our progress. The forum is open to members to advertise job positions available, or being sought, as well as for brief scientific reports, announcements, and for light comedy (in good taste). Members from Africa are especially encouraged to submit articles.

Our next general meeting will be at Experimental Biology 2008,
in San Diego, CA. I look forward to seeing you all there.

On behalf of the Board of Trustees of AABS, I wish you an enjoyable
reading. I also encourage you to regularly visit our web site:
http://www.aabs-inc.org.
To be a part of the communication, you can request to be added to
AABS list sever, by sending e-mail to tsiagbvk@umdnj.edu.

Long Live AABS!
KEEP UP THE SPIRIT!
Vincent K. Tsiagbe
President, AABS, Inc

Dr. Vincent K. Tsiagbe is an Associate Professor at Department of Oral Biology and Department of Pathology, at University of Medicine and Dentistry of New Jersey. He is a Board Member and Executive President of AABS, Inc.

MEMBERSHIP DRIVE

AABS members are encouraged to spread the news of AABS to fellow Biomedical Scientists who are not yet registered members and encourage them to visit our web site, http://www.aabs-inc.org, in order to apply for their membership.

For those who haven't done so, please send your annual dues to the Treasurer at the following address:

Dr. Mohamed A. Bayorh
Department of Pharmacology
Morehouse School. of Medicine
720 Westview Drive, S.W.
Atlanta, GA 30310-14595
United States of America

The membership dues for the current year are:

Faculty / Scientist:	US$50.00
Postdoctoral fellow:	US$30.00
Graduate Student:	US$10.00

Dues for members from Africa

Faculty / Scientist:	US$30.00
Postdoctoral fellow:	US$10.00
Graduate Student:	US$10.00

Donations to our course are always welcome. Remember that your dues and donations are tax-deductible.

FEATURED ARTICLES

Commentary: **PHARMACEUTICALS, NUTRACEUTICALS AND THE SUPPLY CHAIN**

Okezie I Aruoma PhD DSc

The involvement of developing countries in international food trade has transcended ideology from the traditional production of cash crops and raw materials to producing processed or semi-processed food products. Pharmacological, toxicological studies and strict regulatory framework (governing the sale, manufacture, packaging, labeling, importation, distribution and storage of natural health products, botanical drugs, nutraceuticals and functional foods) are important determinants that anchor the supply chain. The African continent is endowed with a great variety of plant species and their use for the purpose of achieving nutritional and therapeutic effects have remained a strong part of the African culture. Medicinal and food plants contain a reservoir of untapped bioactive components that exhibit the potential therapeutic effects on health. Research is needed on the molecular mechanisms of actions of new pharmaceuticals and phytopharmaceuticals as well as plant food and medicinal plant components (food biofactors) and their role in maintaining the integrity of neuronal populations in the central nervous system relevant to infectious, chronic age related neurodegenerative diseases and in sustaining good health.

The supply chain needs to embrace an efficient food safety system that minimizes food losses, increasing health protection, consumer satisfaction, product competition and poverty alleviation. The various factors that determine the supply of botanical drugs and functional nutraceuticals include bioprospecting for new products, low cost sources of existing products, standards that govern the introduction of new products and enhancement of the acceptance of existing products, differentiating products based on the physicochemical properties of the products, product innovation (e.g. new additives to foods, drinks and/or cosmetics). Bioactive molecules and their precursors (largely visualized as being at the very high end of the chemical products value spectrum) in the food plant and traditional medicinal plants are widely used in pharmaceutical and nutraceutical formulations. Future sources of food production and agricultural growth in Africa needs to embrace measures to lift the declining yield in cash crops possibly residing on the use of agricultural extension agents, conventional plant breeding or biotechnology-driven crop improvement can lift cereal yields.

African traditional medicinal plants: Source of bioactive ingredients

African herbal medicine is probably the most ancient and most diversified of all medicinal systems. Unfortunately, the systems of medicines are poorly recorded and remain so to date. Traditional medicine practice that is unequivocally entrenched in the culture of African people resides with numerous varieties of herbal extracts and teas with long professed medicinal values. The demand on natural products will escalate with the emergence of new diseases and this will be further heightened since imported medicine is unsustainable in several African countries under the current economic realities. The traditional, complementary and alternative medicines contain toxic and potentially lethal constituents including aristolochic acids, pyrrolizidine alkaloids, benzophenanthrine alkaloids, lectins, viscotoxins, saponins, diterpenes, cyanogenetic glycosides and furanocoumarins. Among the alkaloids are Asclepias fruticosa from Asclepiadaceae, Gloriosa virescens from Colchicaceae which lead to respiratory disorders and weak heartbeat while Catharanthus roseus from Apocynaceae, Callilepsis laureola from Asteraceae and Adenia gummifera from Passifloraceae results in hypoglycemia. The alkaloids vincristine and vinblastine, isolated from *Catharathus roseus* are potent anti-leukemic drugs. Quinine (from *Cinchona succirubra*) and atropine (from *Atropa belladonna*) have established medical applications. The terpenoids artemisinin (antimalarial), taxol (anticancer), *Digitalis* sterol glycosides (prescribed for congestive heart diseases) and steroidal saponins from yam (precursors for the synthesis of progesterone-like compounds for birth control pills). The review of Gurib-Fakim, (2006) is worth perusing by the reader.

Although there is a wealth of information on traditional uses of plants, investigations on their bioefficacy (and molecular mechanisms of action) are still warranted. Indeed as with other pharmaceutical agents useful for disease prevention, pharmaco-economic analysis of a therapeutic formulation would need to be considered, and the composition of the formulation judged to have improved over time (and hence post-marketing exercise remain critical). The restricted technological advances in several of these developing countries hinder extraction, processing and commercialization of these bioactive constituents. The review of Nwaka (2005) alluded to the set of Millennium Development Goals (MDGs) of the United Nations aimed at alleviating extreme poverty in developing countries (which pledged to halt and begin to reverse the incidence of HIV/AIDS, malaria and other major diseases by 2015. The expected collaboration with pharmaceutical companies will provide access to affordable essential drugs in developing countries can ultimately lead to increased proportion of populations in the developing countries being able to have access to affordable essential drugs on a sustainable basis. The concepts of plant-made pharmaceuticals and the latest advances in the genetic engineering of plants can hold much promise for the production of medicines that are inexpensive and yet abundantly by using a range of different plants as factories to express active medicinal ingredients. Ultimately, how the benefits and risks of plant made pharmaceuticals (hence the botanical drugs and nutraceuticals) are addressed by the respective government's regulation and how this will affect the products that make it to the marketplace and their ultimate success are of great concern to consumers, farmers to health and food production industries.

The drug discovery supply chain (Figure 1) makes pertinent observations. One of the factors of course is availability. The drug must be developed and manufactured. This requires that basic research is properly managed to interface with drug discovery and development. The second major determinant is the accessibility of new drugs in disease-endemic countries. This requires (i) better regulatory systems in developing countries to assess the quality of drugs, (ii) effective distribution systems, (iii) affordability, (iv) sustainable financing, (v) trained healthcare workers and (vi) informed consumers. It is vital to align basic research with translational research in order to produce leads that feed into the drug development pipeline (Figure 1).

Basic research need access to screening facilities and chemical libraries as well as other expertise including focused medicinal chemistry efforts if ideas are to be translated into drug leads. My research focus and interest embraces the search for neuroprotectants and cognitive enhancers with translation research of public health concern. More uniquely, research focus on the role that inflammatory mechanisms have in chronic and infectious diseases and on the dietary factors as prophylactic agents has implications for Africa. The pathophysiology of dementia in advanced age is becoming increasingly understood by revealing the underlying basis of neuropsychological changes with neuroimaging, genetic and pathological features that suggests alterations of the (neuro) vascular regulatory mechanisms may lead to brain dysfunction and disease.

are also being discussed and incubated by various groups. Specific examples include the Product Research and Development in Africa initiative (PRADA) and the initiative for pharmaceutical technology transfer as well as other biotechnology, science and technology initiatives. (Nwaka 2005)

Regulatory status on botanical drugs, nutraceuticals and functional food in the African continent

Traditional medicine represent utilization of whole, fragmented or cut plants, algae, fungi, lichens and botanical preparations from these materials involving extraction, distillation, expression, fractionation, purification, concentration and fermentation. However the manufacturing process, use of solvents/additives, purification and drying techniques, and storage conditions may play a major role on the occurrence of significant amount of contaminants, pesticides, microorganisms, heavy metals, toxic chemicals or solvent residues in the samples. This makes important to define and implement rigorous, standardized manufacturing stages/procedures, quality assurance and quality control techniques. There has been huge emphasis on this by the Food and Agriculture Organization of the United Nations, the World Health Organization, the World Trade Organization (GATT etc.), EMEA and the FDA and the extent of the issues can be best served by visiting their respective website for example. Essentially, government's regulatory mechanisms oversee the analyses of public health problems and their association to the food supply.

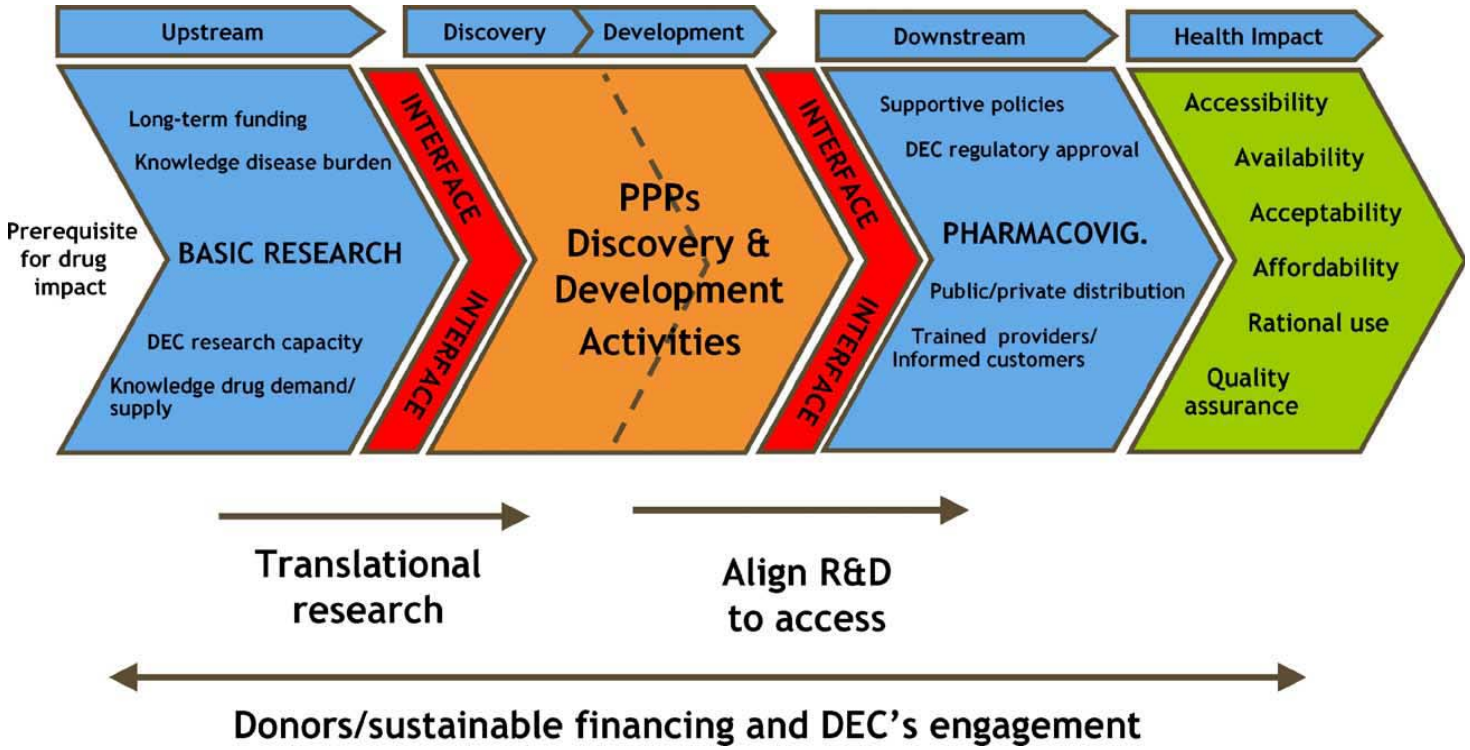

Figure 1. The drug discovery supply chain. In the context of this framework, some African based initiatives for R&D, biotechnology, manufacturing and regulatory development

The Dietary Supplement Health and Education act (DSHEA), introduced in 1984 in the United States provided

consumers ready access to dietary supplements that are safe, effective and of high quality. Several other countries have adopted and amended this act for regulating supplement products. For example, the Natural Health Products regulations was introduced in 2004 in Canada to regulate the sale, manufacture, packaging, labeling, importation, distribution and storage of the nutraceuticals. Although similar legislation relating to nutraceuticals in the European Union is strictly applied, there seems to be no consistency in the legal status of some botanicals across the European countries. For instance, many functional foods or food-derived ingredients may be sold as foods but they may also be considered as herbal medicines registered by full and simplified registration procedures. Similar cases can be recorded across the African continent since there is currently no common regulatory framework to assess these natural health products. Food safety control for public health protection by necessity needs to cover the range of different food chains relevant to a certain food product or product group, including all relevant producers, manufacturing sites and food service establishments within a country as well as those importing into the country. The application of modern international food safety and quality standards (e.g. the safety management systems in the food supply chain: Hazard Analysis Critical Control Points (HACCP), Pre-requisite systems Good Manufacturing Practice (GMP) and the Good Hygiene Practice (GHP)) are primarily geared towards protecting the consumer health.

Further Reading

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Dr. Aruoma is a Professor and Chairman of the Department of Pharmaceutical and Biomedical Sciences, Touro College of Pharmacy, New York, USA Dr. Aruoma obtained his BSc. from the University of Sussex, MSc, PhD & DSc from the University of London, and MBA from the University of Warwick.

ACTIVITY OF PHOSPHODIESTERASES IN NEWBORN LAMB LUNGS.

Brian W. Yue, J. Usha Raj, Basil O. Ibe

ABSTRACT: We have studied the hydrolysis of cGMP and cAMP by major PDE isozymes present in lungs of 3-7 d old lambs. Phosphodiesterases were separated by DEAE cellulose column chromatography of the soluble fraction of lung tissue homogenate. Cyclic nucleotide PDE activity was studied by radiometric assay of the hydrolysis of exogenous cyclic nucleotides at 30^{O}C for 10 min. Rates of hydrolysis (pmol/min/mg protein) of cGMP was 82 ± 15 which was not different from the rate of cAMP hydrolysis of 57 ± 9.0. Hydrolysis of each nucleotide was substrate dose-dependent. Inhibition of hydrolysis of cGMP and cAMP by PDE was dose-dependent for zaprinast, rolipram, and milnirone. Zaprinast was the most effective in inhibiting cGMP hydrolysis, but milnirone and rolipram were more effective in inhibiting cAMP. Our data show that newborn lamb lungs contain a mixed population of PDE isozymes and that cGMP- and cAMP-specific PDEs are the major isozymes present. **Key words:** pulmonary circulation. cGMP, cAMP, zaprinast, rolipram, milnirone.

INTRODUCTION: Cyclic nucleotide phosphodiesterases (PDE) are the enzymes responsible for the hydrolysis of guanosine-3',5'-cyclic monophosphate (cGMP) and adenosine-3',5'-cyclic monophosphate (cAMP). cGMP and cAMP are second messengers that modulate smooth muscle relaxation in vascular, airway, and smooth muscle tissues (1,2, 3). Phosphodiestrases are intracellular enzymes present in several isoforms, designated as cGMP-specific or cAMP-specific. PDE I (Ca2+ calmodulin stimulated), PDE 2 (cGMP-stimulated), PDE 3 (cGMP inhibited), PDE 4 (cAMP-specific), and PDE 5 (cGMP-specific) are five of the major isozymes which have been characterized (4,5,6). The relative activity of each isozyme differs from tissue to tissue. A number of intrinsic modulators such as Ca2+-calmodulin, and tissue levels of cGMP and cAMP regulate PDE activity (7). Thus the level of these cyclic nucleotides in a tissue can be regulated at three levels; by alteration in activity of the synthetic enzymes, by the activity of specific PDE, and by the tissue level of the cyclic nucleotides. We previously showed that, in newborn lamb lungs, PDE activity in arteries is more than that in veins (5,7,8). However, it is not clear that such differences exist in the lung parenchyma of newborn lambs. Therefore our objective in this study was to assess cGMP- and cAMP-specific PDE activities in lungs of newborn lambs. In order to achieve our objective, we first separated the PDE isozymes in newborn lamb lung by DEAE cellulose column chromatography and assayed PDE activity by radiometrics method. Our objective was to understand the activity of PDE isozymes in lung at the newborn age, rather than to compare age-related activity of PDE.

MATERIALS AND METHODS: Five newborn lambs 3-6 days old used in this study were purchased from Nebeker Farms, Santa Monica, CA. This age group was similar to the age of lambs used in our previous studies (8). Ovalbumin, aprotinin, N,N-bis[2-Hydroxyethyl]-2-aminoethanesulfonic acid (BES), EGTA, 3-Isobutyl-1-Methylxanthine (IBMX), 5'-Nucleotidase (from Crotalus atrox venom, 200-500 units/mg protein), trypsin inhibitor (from soybean), cAMP and cGMP standards were purchased from Sigma-Aldrich (St. Louis, MO). DEAE Sephadex A-25 was purchased from Pharmacia Biotech. Rolipram, Milrinone and Zaprinast were purchased

from Biomol Research Laboratories (Plymouth Meeting, PA). Radiolabeled standards: guanosine 3',5'-cyclic phosphate [8-3H]-, ammonium salt, (3H-cGMP), 15 Ci/mmol (555 GBq/mmol) and adenosine 3',5'-cyclic phosphate [8-3H]-, ammonium salt, (3H-cAMP), 60 mCi/mmol (2.22 GBq/mmol) were purchased from Perkin Elmer Life Sciences (Boston, MA). Ecolite liquid Scintillation cocktail and Dithiothreitol (DTT) were purchased from MP Biochemicals (Irvine, CA). Disposable plastic syringes were purchased from Baxter Healthcare Corporation, Chicago, Illinois. All other reagents and chemicals were purchased from Fisher Scientific (Santa Clara, CA). All animal experimentation was approved by the institutional animal care and use committee. **METHODS:** Newborn lambs were killed with an overdose of pentobarbital, the lungs removed and the pulmonary arteries and veins were dissected out. The lung tissues were prepared by homogenization, sonication and centrifugation as previously reported (8,9). Protein concentrations of the cytosol and membrane fractions were determined by the Lowry method (10). The fractions were then frozen in liquid nitrogen and stored at -70 OC until needed. Storage at -70 OC did not affect the enzyme activity. Thawed protein samples were not re-frozen for subsequent use. Column chromatography of cytosolic protein for PDE fractions: Chromatography columns (30 cm x 1.6 cm) were prepared with DEAE cellulose and equilibrated with a 35 mM sodium acetate buffer pH 6.5, containing 1 mM DTT. The PDE fractions were eluted as previously described (9). Sample volumes of 5 ml were collected over a 6 h period. Each fraction was assayed separately for cGMP- and cAMP-specific PDE activity. Fractions with maximum activity for hydrolysis of cGMP or cAMP were used in the rest of the study.

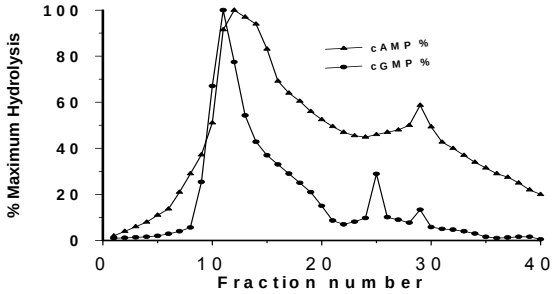

Figure 1 Profile of hydrolytic activity cGMP- and cAMP-specific PDE present in the chromatography fractions. The peak of maximum hydrolysis of cGMP, Peak I, occurred at Fraction #11 while the peak maximum for cAMP, Peak A occurred at Fraction #12. cGMP had two other peaks at, Peaks II and III. cAMP had one other peak, Peak B. Peak B on cAMP corresponded to Peak III on cGMP.

General procedure for PDE assay: All assays were carried out according to previously published methods (8). ***Specific protocols:*** The following specific protocols were performed to determine: a) rate of cyclic nucleotide hydrolysis by PDE; b) effect of substrate concentration on phosphodiesterase catalyzed hydrolysis of a cyclic nucleotide (0.001-10μM); c) dose-response relationships of inhibition of PDE-catalyzed hydrolysis of cyclic nucleotide. The three specific inhibitors: zaprinast, rolipram, and milrinone were used in a concentration range of 0.01-100μM per cyclic nucleotide. In each instance, the protein was pre-incubated with the inhibitor for 10 min and then [3H]-cGMP or -cAMP was added and incubation was continued for 10 min more. ***Data analysis:*** Data are presented as means ± SEM and were analyzed using a un-paired two-tailed Student t-test to detect differences in cGMP- and cAMP-dependent PDE activity. A p value <0.05 was accepted as significant difference.

RESULTS: Figure 1 shows a representative DEAE celllulose column chromatography for PDE present in lung cytosol of the newborn lambs. PDE activity for each chromatogram was normalized to maximum PDE activity. The chromatograph shows two distinct chromatograms for the two cyclic nucleotides. The chromatogram for cGMP shows the major peak of maximum PDE activity at fraction #11 peak I (1 hr after commencement of elution), and two other minor peaks, II and III at fractions #25 and #29 respectively. cAMP chromatogram shows the major peak at fraction #12, peak A, and one minor peak B at fraction #29. Five different lamb lungs were chromatographed. In each case, the major peaks (I for cGMP, and A for cAMP) were used in characterizing the PDE isoforms.

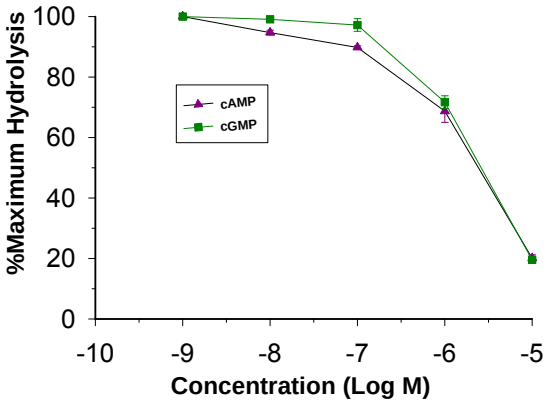

Figure 2 Effect of different concentrations of non-radiolabeled cAMP and cGMP on the hydrolysis of radiolabeled cAMP and cGMP analogs. Data are means ± SEM, n = 5.Protein from fraction #11; cGMP or fraction #12; cAMP was pre-incubated for 10 min with 0μM (buffer alone), 0.001μM to 10μM of cAMP or cGMP or 0μM (buffer alone), Then 0.5μM of the radiolabeled cAMP or cGMP was added and incubation continued for 10 min more. Results are %inhibition relative to control (buffer alone). Both cAMP and cGMP inhibited the hydrolysis of its own radiolabeled analog.

Rates of cGMP and cAMP hydrolysis by PDE in peaks I and A): The rates of cGMP and cAMP hydrolysis (pmol/min/mg protein) by PDE in the newborn lamb lung fractions. were 82 ± 15 for cGMP and 57 ± 9 for cAMP. The rate of hydrolysis of cGMP was not different from rate of hydrolysis of cAMP.

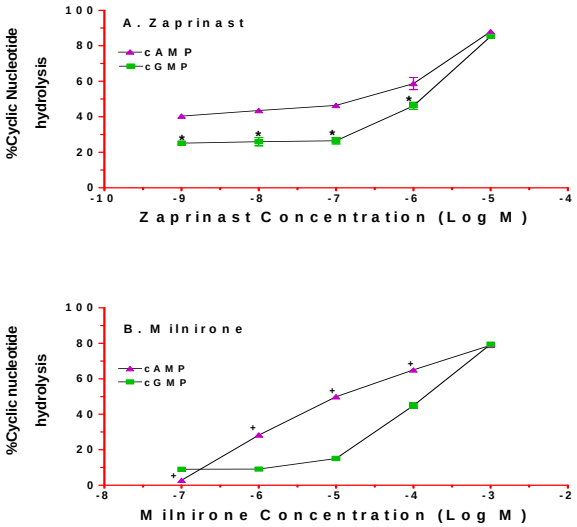

Figure 3 Effect of specific PDE inhibitors: figure 3a, Zaprinast; and figure 3b, Milnirone, on hydrolysis of cGMP and cAMP. Data are means ±SEM, n = 5.Protein from fraction #11; cGMP or fraction #12; cAMP was pre-incubated for 10 min with 0μM of the inhibitor (buffer) for controls or 0.001μM to 10μM for Zaprinast, or 0.1μM to 1000μM for Milnirone. Then 0.5μM of the radiolabeled cGMP or cAMP was added and incubation continued for 10 min more. Results are %inhibition relative to control. Zaprinast was more sensitive in inhibition of cGMP hydrolysis, while Milrinone was more sensitive in inhibition of cAMP hydrolysis. The statistics are; *p<0.05, different from cAMP inhibition; +p<0.05, different from cGMP inhibition.

Effect of non-radiolabeled substrate on PDE hydrolysis of cGMP and cAMP. Figure 2 shows the effect of varying the concentrations of the non-radiolabeled cGMP, and cAMP substrates on the PDE catalyzed hydrolysis of the tritiated cyclic nucleotide analog. PDE activity is expressed as % hydrolysis of the tritiated cGMP or cAMP analog obtained at the lowest concentration of non-radiolabeled analog used. There was a dose-dependent decrease in hydrolysis of the tritiated cGMP and cAMP analog as the concentration of the non-radiolabeled analogs was increased. For cGMP the hydrolysis of the radiolabeled analog in the presence of the non-radiolabeled analog ranged from 95% at 0.01μM to 20% hydrolysis at 10μM. Thus cGMP- and cAMP-specific PDE activity in lungs of newborn lambs were inhibited by increasing concentrations of the substrates, cGMP and cAMP. The inhibitory concentration at 50% maximum (IC50) of cyclic nucleotide substrate self-inhibition of hydrolysis were 2.0 and 2.5μM for cGMP and cAMP respectively.

Zaprinast and Milnirone inhibition of hydrolysis of radiolabeled cAMP and cGMP is concentration dependent. Figure 3 shows the concentration effect of Zaprinast and Milrinone of the hydrolysis of cAMP and cGMP. Both Zaprianst and Milrinone displayed a concentration dependent effect on the hydrolysis of cAMP and cGMP. With Zaprinast, inhibition of both xyclic nucleotides was detectable at nonomolar concentration, but for Milrinone, inhibition was not detectable until 0.1μM concentration of the inhibitor.

Hydrolysis of radiolabeled cyclic nucleotides in the presence of zaprinast, rolipram, and milrinone and IBMX. Table 1 summarizes the calculated IC50 values, in micromolar (μM), of inhibition by zaprinast, a cGMP-specific Type 5 PDE inhibitor, Rolipram a cAMP-specific Type 4 PDE inhibitor, and milrinone an inhibitor of cGMP-inhibitable PDE, on the PDE catalyzed hydrolysis of cGMP and cAMP. The effective concentrations of zaprinast, rolipram, and milrinone necessary to inhibit PDE catalyzed hydrolysis of cGMP and cAMP by 50% (IC50) in the newborn lamb lung tissues were calculated from concentration-response plots as shown in figure 2 for cGMP and cAMP. Zaprinast was ten-fold more effective in inhibiting cGMP hydrolysis than cAMP hydrolysis. However, rolipram and milrinone were more potent in inhibiting cAMP hydrolysis than cGMP.

Metabolites	Zaprinast	Rolipram	Milrinone
cGMP	15.0	50.0*	90.0*
cAMP	150.0+	2.5+, *	6.0+, *

Figure 3 shows the effect of 100μM of zaprinast, rolipram, milrinone, and IBMX on PDE catalyzed hydrolysis of cGMP and cAMP. Zaprinast inhibited hydrolysis of cGMP by 92%, significantly more than the 45% inhibition of hydrolysis of cAMP. On the other hand, rolipram and milrinone inhibited cAMP hydrolysis more than cGMP hydrolysis. The values in %inhibition were as follows rolipram: cAMP, 71 ± 6 and cGMP, 26 ± 10; milrinone: cAMP, 71 ± 5 and cGMP, 42 ± 9. However, there was no difference in inhibition PDE activity by the non-specific inhibitor, IBMX.

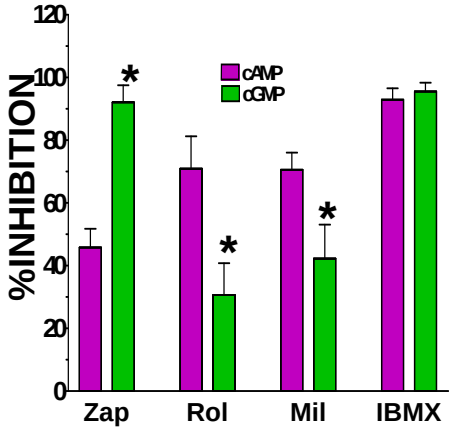

Figure 4 Effect of different PDE inhibitors; Zaprinast (ZAP), Rolipram (Rol), Milrinone (Mil), and 3-isobutyl-1-methyl-xanthine (IBMX), on the hydrolysis of cGMP and cAMP. Data are means ±SEM, n = 5. Protein from fraction #11; cGMP or fraction #12; cAMP was pre-incubated for 10 min with 100μM of the inhibitor or with the buffer for controls. Then 0.5μM of the radiolabeled cGMP or cAMP was added and incubation continued for 10 min more. Results are %inhibition relative to control. Zaprinast was more sensitive in inhibition of cGMP hydrolysis, while Milrinone was more sensitive in inhibition of cAMP hydrolysis. The statistics is; *p<0.05, different from cAMP inhibition.

DISCUSSION: Vascular and airway smooth muscle relaxation is mediated by cGMP and cAMP via the respective protein kinases (11,12,13). Tissue levels of these mediators are in part dependent on the activity of PDE,

which is the catabolic enzyme (3). We studied activity of PDE isoforms in lung of newborn lambs, after DEAE cellulose column fractionation, by examining the response of this enzyme to increasing concentrations of substrates and the effect of specific PDE inhibitors. We found that cGMP-, and cAMP-specific PDEs are the predominant PDE isoforms in newborn lamb lungs.

Cyclic nucleotide PDE activity in newborn lamb lungs. There was no difference in rate of hydrolysis of cGMP and cAMP in lung cytosol of the newborn lambs. However, we found that increasing the concentration of the cyclic nucleotide, in the presence of a constant amount of the respective tritiated analog, led to increased inhibition of cGMP and cAMP hydrolysis in the tissue, demonstrating a concentration-response effect. We further tested the specificity of either cGMP-specific or cAMP-specific PDE to inhibit the hydrolysis of each other by cross stimulation. We found that neither cGMP nor cAMP was effective in producing a concentration-response effect in the inhibition of the other cyclic nucleotide isolated from our separation process. For instance, 10μM of cAMP produced only 15 ± 2.5% (n = 4) inhibition of cGMP hydrolysis, whereas 10μM of cGMP inhibited its own hydrolysis by more than 90%. Similarly, 10μM of cGMP inhibited cAMP hydrolysis by only 18.8 ± 7.9%, while 10μM of cAMP inhibited its own hydrolysis by more than 80%. We can infer from these results that, although cross-activation of cGMP and cAMP do occur (14), each of the cyclic nucleotides is more sensitive and more specific in inhibiting its own hydrolysis by the PDE present in newborn lamb lungs. It also shows that the chromatography process was successful in separating the two classes of cyclic nucleotide PDE.

Effect of PDE inhibitors on PDE activity: There are at least 10 classes of phosphodiesterases present in various organs and tissues, and with at least 2 isoforms in each class (4, 6). In the present study, we found that cyclic nucleotide PDEs present in newborn lamb lungs were inhibitable by the specific PDE inhibitors; zaprinast a type V PDE inhibitor, rolipram a type IV PDE inhibitor, and milrinone a type III cGMP inhibitable cAMP inhibitor (4;6). It has been shown that cGMP and cAMP play important roles in regulation of airway and vascular smooth muscle tone in models of some pulmonary diseases such as asthma and pulmonary hypertension (15,16,17). PDE inhibitors elevate cyclic nucleotide levels indirectly by inhibiting their catabolism (13,18,20,22), and the lung contains a rich pool of PDE 5 as well as PDE 4 (6). In our study, we found that Zaprinast was more sensitive in inhibiting cGMP hydrolysis while rolipram and milrinone were more sensitive in inhibiting cAMP hydrolysis. The findings are in accordance with the inhibitory properties of these compounds (13), and further support the identity of the PDE fractions we studied.

In summary, we have shown that cGMP- and cAMP-specific PDEs are the major PDEs present in the newborn lamb lung. Although there is no difference in the rates of PDE catalyzed hydrolysis of cGMP and cAMP, we found significant differences in the inhibition of cGMP- and cAMP-specific PDE. The newborn lung is susceptible to the pathology of persistence pulmonary hypertension (23), of which the causes are not well understood, but it is known in persistent pulmonary hypertension, activities of PDE 4and PDE 5 are high (REF). Also the biochemical mechanisms underlying the regulation of pulmonary hemodynamics in the newborn period are not well delineated, although a dysregulation of nitric oxide-cGMP pathway plays a significant role in modulating lung blood flow in the newborn period by regulating pulmonary vascular resistance (19, 20,21). Recently, it was demonstrated that PPHN in the neonatal lamb was characterized by high levels of cGMP-specific PDE, and the condition of PPHN was ameliorated by use cGMP-specific PDE inhibitors (22, 25). Furthermore, it has been demonstrated that endogenous cAMP mediated lung liquid absorption in very newborn lambs aged 0-2 weeks, but not in juveniles 6-12 weeks old (24). The results of our study would suggest that since cGMP and cAMP are major pulmonary vasorelaxants in lungs of newborn lambs, use of cGMP- and cAMP-specific PDE inhibitors in situations where PDE levels are high during the newborn period, will increase the levels of endogenous cGMP and cAMP and thereby reduce the incidence of PPHN while at the same time facilitating lung liquid absorption. In addition, since there was no difference in the cGMP- and cAMP-specific PDE activities, our data suggest that sensitivity to inhibition rather activity is more important in controlling PDE effect in newborn lung of newborn lambs.

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PROFESSIONALS IN THE NEWS

Dr Rotimi, heads U.S. genetic research center

UNITED STATES (U.S.) government-owned National Institutes of Health (NIH) has named a Nigerian-born researcher as director of its new medical research center which would be known as the NIH Intramural Centre for Genomics and Health Disparities (NICGHD).

Dr Rotimi is a graduate of the University of Benin, where he earned a BS degree in Biochemistry in 1979. He earned a MS degree in epidemiology at the University of Mississippi, 1983, and a second MS degree in Public Health (MPH) from the University of Alabama, at Birmingham in 1988 followed by a PhD in Epidemiology in 1991. With over 80 published papers, Dr Rotimi is a global leader in genetic research. He started his academic career in 1992 as Assistant Professor at the Loyola University, Chicago, becoming an Associate Professor in 1996. He joined Howard University, an historically black university where he became Director of Genetic Epidemiology in 1999 and a full professor in 2003. He joined the NIH where he rose to become a Senior Investigator and Acting Director four years ago. He was elected Co-Chairman of the American Diabetic Association in 2001 and the President of the African Society of Human Genetics in 2004. Describing him as the "internationally renowned genetic epidemiologist", a U.S. government statement announced Dr. Charles N. Rotimi as the new director of the new center located in Maryland. The historic announcement was received with much enthusiasm in the growing community of Nigerian, African academics and intellectuals in the U.S.

The NICGHD would be a "venue for research about the way populations are impacted by diseases, including obesity, diabetes and hypertension." Under Rotimi's leadership, the new center is also expected to provide "training opportunities for students and established scientists from developing countries and from minority groups in the United States. According to the US government statement, "a key focus of Dr. Rotimi's research is understanding the triangular relationship between obesity, hypertension, and diabetes, which together account for more than 80 per cent of the health disparity between African Americans and European Americans."

"This new center will be an NIH resource to help move research related to the complex factors underlying health disparities into the 21st century," said NIH Director, Elias A. Zerhouni, MD. "Synergy among the centre's genetic and genomic researchers and disease experts in existing NIH research programs will advance our understanding of health disparities for the benefit of minority groups and all Americans." Genomic research has shown that the genomes of any two individuals are very similar. However, the subtle genomic differences that remain, contribute to unique biological traits, such as hair and eye color, as well as to the susceptibility to diseases and individual responses to drugs. Additional factors contribute to health and disease, including diet, exercise routines and access to medical care. Genetic epidemiologists study genetic differences in combination with environmental factors to assess disease susceptibility and resistance among individuals and population groups.

Dr. Rotimi is currently "engaged in the first genome-wide scan of an African American cohort, with the goal of identifying genes associated with obesity, hypertension, diabetes, and metabolic syndrome. More than 2,000 participants from multigenerational African American families are enrolled in this large-scale genetic epidemiology study." He is also extensively involved in a number of genetic epidemiology projects being conducted in several African countries, China, and in the United States. These projects included the Africa America Diabetes Mellitus Study; the Howard University Family Study; the Genetics of Obesity in Blacks Study; the Black Women Health Study; Consent in Genetic Research; An International Trial; the Engagement of African Communities for the International HapMap Project; and the Genetic Basis of Podoconiosis, a foot-disfiguring disease affecting some who work barefoot in volcanic soils.

The Board of Trustees, on behalf of members of AABS congratulate Dr Charles Rotimi for this laudable and historic achievement and wish him the best of luck in the new assignment.

Laolu Akande in New York originally reported the highlights of this news item at http://www.tribune.com.ng/index.html.

Kunle Odunsi, MD, PhD, a Professor at School of Medicine & Biomedical Sciences, University at Buffalo, has been elected to the Executive Committee of the Cancer Vaccine Consortium

The Cancer Research Institute Cancer Vaccine Consortium is the leading initiative on cancer vaccine, immunotherapy discovery and development. The Consortium members include many of the world's most innovative pharmaceutical, biotechnology, and academic institutions.

Dr. Odunsi, a member of AABS, is one of a group of twelve executive committee members, selected from experienced

leaders who represent the various interests of the CVC membership.

The Board of Trustees, on behalf of members of AABS, wish to congratulate Dr. Odunsi for his laudable achievement.

More information, visit:
http://www.cancerresearch.org/ConsortiumLeadership.html

HEALTH NEWS FLASH

Compiled by Momoh A. Yakubu, PhD

Use Tamiflu And Loss Your Mind. Neuropsychiatric warning for users of Tamiflu has been issued by FDA. The FDA has mandated the manufacturer of oseltamivir phosphate (Tamiflu) -Roche Laboratories to revise the product label and include a warning on a possible Neuropsychiatry episodes following ingestion of this drug. This warning was consequence on the recommendation of the FDA's Pediatric Advisory Committee. It was observed that patient with influenza taking Tamiflu show delirium and abnormal behavior, which could lead to injury and possible death. This observation was noticed following post marketing surveillance and report of the product. Most of the reported events happen in Japanese children taking the medication. It is still not very clear if the abnormal behavior was due to the medication, the label warning caution physicians to monitor their patients for unusual behavior and report it to FDA.
Oseltamivir is indicated for use in people showing symptoms caused by the flu virus (influenza). It help lessen severity of symptoms associated with flu (e.g. stuffy nose, cough, sore throat, fever/chills, aches, and tiredness) and shortens the recovery time. This medication can also used to prevent the flu if you have been exposed to someone who already has the flu -sick household member or workers. Oseltamivir phosphate acts by flu virus growth inhibition and multiplication. Use of Tamiflu is not a substitute for the flu vaccine and it is not indicated for infants less than a year old.

Vaccine for Hypertension? Scientists are tinkering with the possibility of developing a vaccine against hypertension. Despite the fact that there are several safe antihypertensive agents available and in therapeutic use with few side effects, sustained control of blood pressure is still not being attained in several patients. The lack of sufficient blood pressure control often leads to complications such as end organ damage –renal failure, stroke etc. To alleviate this problem in patients with uncontrolled hypertension, researchers are now exploring the feasibility of a vaccine targeting one of the pathways to which this pathology has been associated -angiotensin II. Several antihypertensive agents target the angiotensin system, and they are known to be effective in treating some patients. The angiotensin II is the new target for the vaccine development against hypertension. The vaccine -CVT006-AngQb, a virus-like particle linked to the endogenous peptide angiotensin II has been tested in patients with hypertension in Europe. In a short study (*Tissot AC et al.* Lancet *2008 Mar 8; 371:821*) reported by the manufacturer of the vaccine from Europe reported a modest reduction in blood pressure in hypertensive patients compared to placebo. The subjects received three subcutaneous injections either 100 µg or 300 µg of CVT006-AngQb, at 0, 4, and 12 weeks, or placebo and ambulatory blood pressure (ABP) measured at baseline and 2 weeks after the last injection. No serious adverse reaction to this vaccine was reported except mild transient reactions at the site of injection and flu like symptom in a few which lasted for 2 days.

This very preliminary finding indicates the possibility for effective vaccination against endogenous vasoactive agent can be exploited for therapeutic purposes. It further shows that vaccine targeted against this peptide could be safe for use in patients with hard to control blood pressure with conventional medication. However, further studies are required to determine the extent of the beneficial effects of this vaccine. In addition, to determine how it will affect the autoimmune responses of patients that are already immune compromised by the hypertensive condition.

Depression: A Risk Factor for Stroke? It is known that depression is a risk factor for heart disease while depressive symptom has been linked to increased morbidity and mortality. However, it is not known whether either depression or psychological distress increases the risk for stroke. In a recent study (*Surtees PG et al.* Neurol *2008; 70:788*) reported that increase in psychological distress is associated with elevated stroke risk. However, strategies that mediate stress may have a long-term health benefit, but patient education about the possible advantages of exercise, meditation and keeping a healthy mind might ward off stroke.

Lose Weight and Your Peace Mind! A new a selective antagonist of the cannabinoid type I receptor (Rimonabant) has been reported to result in more weight loss compared to conventional agents (*Christensen R et al.* Lancet *2007; 370:1706*). Rimonabant is approved for weight loss use in Europe, has been reported to result in significantly greater weight loss than placebo (difference, 4.7 kg). They were more likely to achieve at least 10% weight loss within the treatment period. Rimonabant recipients were more likely than controls to drop out because of treatment-emergent depressive disorders and anxiety. In addition, greater adverse effects were reported in older individuals and depressed mood in those with higher triglyceride levels. The FDA has declined to approve it for use in the U.S. at this time as it has raised major concerns about the safety of this drug.

Risk of Death Stops ACCORD Trial: The National Heart, Lung, and Blood Institute have stopped a treatment arm of the ongoing Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. The early termination of trial was due to an increased risk for death among patients assigned to intensive glucose-lowering therapy NHLBI stated in a February 6, 2008 press release. The participants in this 77

North American sites randomized to treatment aimed at achieving HbA_{1c} levels of <6.0% are now aimed at attaining a target HbA_{1c} level of 7.0% to 7.9%, the same as participants in the control group. Other strategies of the trial such as management of cholesterol and hypertension will continue as planned.

This decision was predicated on the recommendation of the Safety Monitoring Board of ACCORD after it was discovered that 257 patients in that group had died, compared with 203 in the standard therapy group. Preliminary analyses have found no association of the mortality increase with any specific drug or drug combination. All participants in the ACCORD study have type 2 diabetes and either coronary heart disease or at least two risk factors for adverse cardiovascular events.

Evidence Supports Beneficial Diuretics Therapy - Especially in Black Patients: New research shows that in people with high blood pressure as part of metabolic syndrome, a cluster of conditions that increases the risk for heart disease, diuretics offer greater protection against cardiovascular disease, including heart failure, and are at least as effective for lowering blood pressure as newer, more expensive medications. The findings run counter to current medical practices that favor ACE-inhibitors, alpha-blockers, and calcium channel blockers for treatment of high blood pressure in those with metabolic syndrome. In addition, the results provide important new evidence supporting the use of diuretics for initial blood pressure-lowering therapy in black patients with metabolic syndrome.

These findings are particularly important for patients with metabolic syndrome because many doctors currently prescribe alpha-blockers, calcium channel blockers, and ACE-inhibitors due to their more favorable short-term effects on blood sugar and blood cholesterol levels. However, this new analysis shows that diuretics are better at preventing cardiovascular disease and thus does not support the selection of the newer drugs over diuretics for preventing poor health outcomes related to hypertension or for lowering high blood pressure, said Elizabeth G. Nabel, M.D., director, NHLBI.

This latest analysis shows that even among men and women with metabolic syndrome, and for black and non-black (Caucasians, Hispanics, Asians/Pacific Islanders and American/Alaskan Natives) participants, the less costly diuretics consistently control blood pressure, are equally beneficial in preventing heart attack and coronary heart disease death. They are also more beneficial than newer medications in preventing one or more other forms of cardiovascular disease including heart failure and stroke.

Dr. Yakubu is the Editor of the BioMed Scientist. He is a Senior Scientist/Associate Professor in the Center for Cardiovascular Diseases, Texas Southern University College of Pharmacy and Health Sciences, Houston, TX-USA.

AABS ANNOUNCEMENTS:

AABS General Meeting 2008
DATE: April 8, 2008
VENUE: San Diego MARRIOTT HOTEL & MARINA
ROOM: SANTA ROSA
Located on the 1st Floor, South Tower with close proximity to the San Diego Convention Center.

ADDRESS: *333 WEST HARBOR DRIVE, SAN DIEGO, CA 92101 7700, PHONE: 619 234 1500*

TIME:
4:30 pm – 5:00 pm REGISTRATION / COFFEE
5:00 pm – 6:30 pm GENERAL MEETING
6:30 pm – 8:30 pm BOARD MEETING

OPPORTUNITIES FOR RESEARCH AND TRAVEL:

Minority Access to Research Careers (MARC) http://marc.faseb.org/

MEETING ANNOUNCEMENTS

2008 APS Intersociety Meeting: The Integrative Biology of Exercise V, September 24-27, 2008, Hilton Head, South Carolina, Abstract Deadline: June 2, 2008
http://www.aps.org/

The XXIVth International Symposium on Cerebral Blood Flow and Metabolism & The IXth International Conference on Quantification of Brain Function with PET.June 29-July 3, 2009. Chicago, IL, USA.
http://www.kenes.com/brain/

22nd Annual Symposium of The Protein Society San Diego, CA July 19-23, 2008
www.proteinsociety.org/

SUMMER RESEARCH CONFERENCES
http://src.faseb.org/

IASP 12th World Congress on Pain: Glasgow, Scotland, UK, August 17-22, 2008.
http://www.iasp-pain.org/

23rd AACVPR Annual Meeting: Indianapolis, IN. Sept. 18-20, 2008
http://www.aacvpr.org/

Society of General Physiologists 62nd Annual Meeting and Symposium (SGP): *Calcium Signaling and Disease*, Woods Hole, MA. Sept 3-7, 2008.
http://www.sgpweb.org/symposium2008.html

1st International Symposium on Audible Acoustics in Medicine and Physiology: West Lafayette, IN. September 8-9, 2008:
https://engineering.purdue.edu/Acoustics/

Cardiovascular & Respiratory Systems Modeling: From Cell to Organ: Seattle, WA, September 8-15, 2008. http://www.physiome.org/

Workshop on the Biology of Signaling in the Cardiovascular System: Cape Cod, MA. Sept 11-14, 2008.; http://www.navbo.org/BSCVS /

Workshop on Mathematical Modeling of Human Metabolism and Body Weight Regulation: Bethesda, MD. Sept. 27-28, 2008.
http://www.mitacs.ca/conferences/HMBW/

XXII International complement Workshop*:* Basel, Switzerland._Sept. 28-Oct. 2, 2008. **Information:** Email: info@akm.ch; Internet: http://www.akm.ch/ICW2008/

The 2nd World Congress on Controversies in Diabetes, Obesity and Hypertension (CODHy): Barcelona, Spain October 30-November 2, 2008.
http://www.codhy.com/

XXX World FIMS Congress of Sports Medicine: Barcelona, Spain. November 18-23, 2008.
http://www.aps.org/

4th European Congress of the International Federation for Medical and Biological Engineering: Antwerp, Belgiu. Nov. 23-27, 2008.
http://www.mbec2008.be/

The 11th World Congress on Controversies in Obstetrics, Gynecology & Infertility. COGI)*:* Paris, France, Nov. 27-30, 2008.
http://www.comtecmed.com/

American Society for Matrix Biology (ASMB) 2008 National Meeting: San Diego, CA December 7-11, 2008.
http://www.asmb.net/

THE AMERICAN ASSOCIATION OF IMMUNOLOGISTS AAI 2008 COURSES

AAI 2008 Introductory Course in Immunology. June 20 - 26, 2008 -- University of Pennsylvania, Philadelphia. Deadline : June 4, 2008
http://www.aai.org/Intro_Course/2008/Program.html

AAI 2008 Advanced Course in Immunology. July 19-24, 2008
University of Minnesota/Minneapolis Campus.
Deadline : June 4, 2008
http://www.aai.org/Adv_Course/2008/Program.htm

Financial support for underrepresented minority scientists is available for both AAI Immunology Courses through the FASEB MARC Program.
http://marc.faseb.org/

GORDON RESEARCH CONFERENCES:

Brain Energy Metabolism & Blood Flow: August 17-22, 2008 Proctor Academy, Andover, NH.
http://www.grc.org/

Synaptic Transmission: July 27-Aug t 1,2008.
University of New England, Biddeford, ME.
http://www.grc.org/

RELOCATIONS OF AABS MEMBERS

Dr. Okezie I Aruoma has joined the Touro College of Pharmacy as a Professor and Chairman of the Department of Pharmaceutical and Biomedical Sciences, New York, USA. He moved from London South Bank University, London, UK.

Dr. Ashiwel S. Undieh has assumed the position of Professor of Neuropharmacology and Chairman of the Department of Pharmaceutical Sciences at the Jefferson School of Pharmacy, Thomas Jefferson University, Philadelphia. He moved from Baltimore, Maryland, USA.

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