

THE RECEPTORS FOR THE PHORBOL ESTER TUMOR PROMOTERS: KEY PLAYERS IN SIGNAL TRANSDUCTION AND CARCINOGENESIS

Marcelo G. Kazanietz, Ph.D., Associate Professor of Pharmacology

Diacylglycerol signaling, phorbol esters and cancer

One of the key second messengers generated upon activation of seven-transmembrane and tyrosine kinase receptors is diacylglycerol (DAG), a lipid produced directly by the action of phospholipase C isozymes or indirectly by the phospholipase D/phosphatidic acid (PA) pathway. DAG is a relatively simple and highly flexible molecule that is transiently generated in membranes and that activates one of the major intracellular signaling pathways: the protein kinase C (PKC) pathway. Understanding the regulation and function of signaling molecules requires the use of pharmacological and molecular approaches. In the case of PKC, the use of pharmacological agents proved to be critical to determine their involvement in cellular functions. We have been fortunate that Mother Nature has provided us with a family of potent and selective PKC activators that mimic DAG function: the phorbol esters. The overall goal of our laboratory is to elucidate the nature and function of the receptors for these natural products and the second messenger DAG.

Why is it so important to understand the biological and pharmacological

properties of the DAG/phorbol ester receptors? A main reason is that phorbol esters are very potent tumor promoters in the mouse skin model of multistage carcinogenesis. Through the years it became clear that PKC is a key regulator of cell proliferation, differentiation and apoptosis. In addition, phorbol ester activation of PKC regulates oncogene action (for example the Ras oncogenic pathway), which makes PKC an attractive target for pharmacological intervention in cancer chemotherapy. Moreover, changes in the expression of PKC isozymes have been observed in numerous types of cancer, including colon, prostate and breast cancer. However, the picture is not simple because PKC is a family of at least 10 isozymes (Figure 1) with differential intracellular distribution and regulation, and at least 8 PKC isozymes are phorbol ester/DAG responsive. A single cell expresses at least 5 PKCs, which may have either opposite or overlapping functions. Thus, one of the challenges in the field is to elucidate the role of individual PKC isozymes in cellular function, and more importantly, how they relate to malignant transformation and multistage carcinogenesis.

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PLATELETS: STICKING TOGETHER WHEN THE NEED ARISES

Lawrence F. (Skip) Brass, M.D., Ph.D., Professor of Medicine, Pharmacology and Pathology

What are platelets and how do they work? More importantly, why should anyone care? Cardiovascular disease remains the leading cause of deaths in the United States, but despite what the cardiologists will tell you, it's not atherosclerosis that kills, it's platelets – the rapid accumulation of activated platelets on a ruptured plaque leading to the abrupt closure of an already narrowed artery in the coronary or cerebral circulation. In other words, the same cells that under other circumstances keep you from bleeding can block key arteries, leading to tissue ischemia, injury and death. I've been fascinated by platelets since I was a graduate student in an MD-PhD program. Since then, I've had the good fortune to work with a succession of really terrific postdocs, graduate students and research specialists. Together we've tackled some of the key issues in the biology of platelets with the biggest being: How do they become appropriately activated at sites of vascular injury and how do they avoid being inappropriately activated when activation is unwarranted? The approaches that we have used (and continue to use) range from biochemical studies on isolated human platelets to whole-animal studies on genetically-modified mice. Much of the work has focused on events mediated by G proteins and G protein coupled receptors, trying to understand how diverse platelet agonists produce responses in platelets. Recently, we have also tackled an underserved, but essential issue: How do platelets remain activated long enough for hemostasis to occur and for wound healing to begin? In this case,

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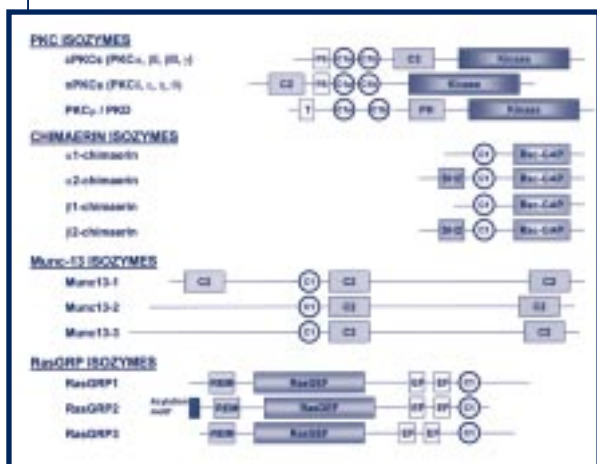


Figure 1. Structure of PKC isozymes and novel phorbol ester receptors. cPKCs, “classical” or calcium-dependent PKCs; nPKCs, “novel” or calcium-independent PKCs; PS, pseudosubstrate domain; PH, PH domain; SH2, SH2 domain; T, transmembrane domain; Rac-GAP, Rac GTPase-activating protein domain; REM, Ras exchange motif; RasGEF, region with homology to the nucleotide exchange factor domain of Sos; EF, EF hands. The C1 domain is responsible for the high affinity binding of phorbol esters and DAG.

PKC and prostate carcinogenesis

A main area of research in our laboratory involves the study of PKC isozymes in prostate cancer progression. Although phorbol esters stimulate mitogenesis in several cell types, PKC activators reduce cell proliferation or induce apoptosis in prostate cancer cells. For example, a single application of phorbol 12-myristate 13-acetate (PMA) to androgen-dependent LNCaP cells promotes apoptosis as assessed by DNA laddering, DAPI staining or flow cytometry analysis. In order to elucidate which members of the PKC family are involved in such effect, we have used an adenoviral approach to overexpress individual members of the PKC family or mutated forms of PKC isozymes. These experiments provided strong evidence PKC α (a member of the “classical” or calcium-dependent PKCs) and PKC δ (a member of the “novel” or calcium-independent PKCs) are pro-apoptotic kinases in LNCaP cells. Analysis of the signaling pathways reveals that the survival molecule Akt (protein kinase B) and the p38 MAPK pathway are key mediators of the phorbol ester effect. Another important finding is that PMA promotes the subcellular redistribution or “translocation” of PKC α and PKC δ to the plasma membrane. We have strong evidence that allosteric activation of these kinases in the membrane rather than the release of a constitutively active fragment by caspase cleavage is required for the apoptotic effect of PMA (Figure 2). Among the main goals of the laboratory are the elucidation of the PKC substrates and effectors of individual PKC isozymes, as well as the regulation of PKC signaling by androgens in prostate models. The development of transgenic mice for PKC isozymes will be critical to understand the functions of PKCs in normal prostate function and prostate carcinogenesis.

Novel phorbol ester/DAG receptors: the C1 domain connection

A second area of interest in our laboratory relates to the “non-PKC” family of phorbol ester/DAG receptors. In recent years, the traditional view of PKC as the sole receptor for the phorbol esters has been challenged with the discovery of proteins unrelated to PKC that bind DAG and phorbol esters with high affinity, suggesting a high degree of complexity in the signaling pathways activated by DAG. A unique feature of these novel phorbol ester receptors is that, unlike PKC isozymes, they do not have a kinase domain in their structure. These novel “non-kinase” phorbol ester receptors include chimaerins (a family of Rac GTPase Activating Proteins or Rac-GAPs), RasGRPs (exchange factors for Ras/Rap1) and Munc13 isoforms (scaffolding proteins involved in exocytosis). What do all these proteins have in common? They all share a 50-51 amino acid motif named C1 domain, which was identified as the DAG/phorbol ester binding site (see Figure 1). Thus, the use of phorbol esters as specific activators of PKC isozymes in cellular models is questionable.

In the last years we have focused on the chimaerins, phorbol ester receptors that accelerate the hydrolysis of GTP from small GTPase Rac, a member of the Ras superfamily. This novel family of phorbol ester receptors resembles a “chimaera” between the regulatory region of PKC isozymes (the C1 domain) and BCR, the Breakpoint Cluster Region protein involved in Philadelphia chromosome translocation in chronic myelogenous leukemia (Figure 3). *n*-Chimaerin (later renamed α 1-chimaerin) was the first isoform cloned, and it is highly expressed in brain. Three additional isoforms (α 2-, β 1- and β 2-chimaerin) were isolated later. These proteins are alternative spliced products from the α - and β -chimaerin genes.

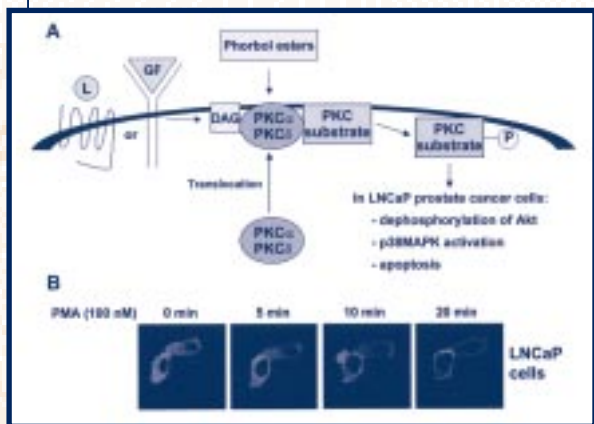


Figure 2. Panel A. Phorbol esters activate PKC isozymes in LNCaP prostate cancer cells. As a consequence of activation, PKC isozymes redistribute or “translocate” to the plasma membrane, where they phosphorylate specific PKC substrates. In LNCaP prostate cancer cells, phorbol ester activation of PKC α and PKC δ leads to apoptosis. Panel B shows the translocation of GFP-PKC α to the plasma membrane by a phorbol ester (PMA) in LNCaP cells.

A thorough characterization of $\beta 2$ -chimaerin as a phorbol ester receptor showed important similarities with PKC isozymes and also striking differences. Scatchard plot analysis revealed that $\beta 2$ -chimaerin binds [3 H]PDBu (phorbol 12, 13-dibutyrate) with high affinity. The K_d is approximately 1 nM, which is in the same range as the K_d 's of cPKCs and nPKCs for this radioligand. However, tumor promoters of the mezerein family showed a marked preference for PKC α relative to $\beta 2$ -chimaerin in binding assays. Unique interactions occur within each C1 domain, as we have assessed by molecular modeling. Studies using GFP- $\beta 2$ -chimaerin revealed that phorbol esters such as PMA translocate this Rac-GAP protein to the plasma membrane and to the perinucleus in a PKC-independent manner, and co-localization of $\beta 2$ -chimaerin with a Golgi marker was observed. Mutagenesis analysis revealed that the C1 domain in $\beta 2$ -chimaerin is critical for targeting this Rac-GAP protein to membranes. Interestingly, we found that $\beta 2$ -chimaerin associates with Rac1 at the plasma membrane, which may lead to its inactivation and inhibition of Rac-mediated signaling. Our search for chimaerin-interacting proteins using yeast two-hybrid revealed that chimaerins associate with Tmp21-I (p23), a Golgi/ER protein involved in sorting/trafficking. The C1 domain is essential for this association, thereby implying a novel function for this domain in protein-protein interactions in addition to its role in lipid and phorbol ester binding. It remains to be explored how redistribution of chimaerins to the perinuclear region relates to Rac signaling. Importantly, a large pool of Rac1 in its inactive, GDP-bound form is located in the perinuclear region. Therefore, it is tempting to speculate that $\beta 2$ -chimaerin and/or other chimaerin isoforms also play a role in the maintenance of the perinuclear Rac in an inactive state before this GTPase moves to the plasma membrane.

Our current working hypothesis is that phorbol esters (and therefore DAG as a second messenger) can regulate chimaerin activity in addition to PKC signaling. This is critical for cancer research because Rac1, the target for chimaerins, is an important player in actin cytoskeleton reorganization, control of gene expression and cell cycle, as well as in the regulation of adhesion, migration, and metastasis (Figure 3). Clearly, a high degree of complexity exists in the pathways downstream of DAG generation. Our challenge is to elucidate such complex signaling mechanism with the ultimate goal of finding novel targeting molecules for cancer therapeutics using cellular, genetic and pharmacological approaches.

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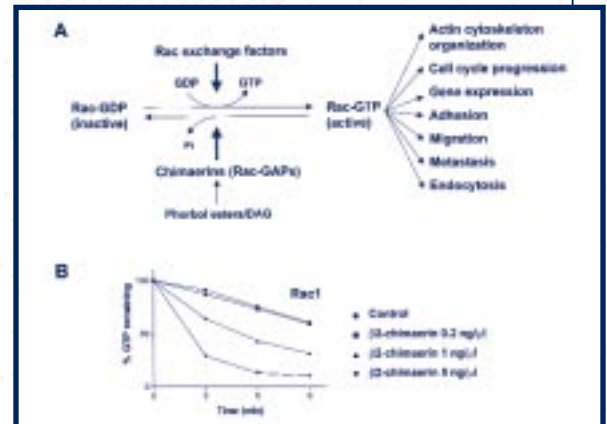


Figure 3. Panel A. Chimaerins have GAP (GTPase activating protein) activity for the small GTPase Rac. Rac cycles between an "on" and an "off" state. Rac exchange factors switch the "off" (GDP-bound) to the "on" (GTP-bound) state, leading to Rac activation. GAPs (such as chimaerins) accelerate GTP hydrolysis leading to Rac inactivation. Panel B. Rac-GAP activity of $\beta 2$ -chimaerin.



Marcelo G. Kazanietz, Ph.D., is an Associate Professor of Pharmacology and a member of the Center for Experimental Therapeutics. He graduated from University of Buenos Aires (Argentina), and after a 5-year post-doctoral at the National Cancer Institute, NIH, he joined the Department of Pharmacology in 1995. His main research interests are the mechanisms of signal transduction in carcinogenesis, focusing on protein kinase C (PKC) and novel receptors for the phorbol ester tumor promoters and diacylglycerol.

our work has focused on a family of receptor tyrosine kinases that we've found on the surface of platelets, and it is that story which I will summarize here. Most of this work was initiated and completed by Nicolas Prevost, a graduate student from the University of Paris, with contributions from Dr. Donna Woulfe (a Pharmacology Graduate Group alumna), Takako Tanaka, and very recently, Ryan Fortna and Wenying Jian.

Platelet activation. Formation of the hemostatic plug at sites of vascular injury begins with the arrest of circulating platelets on exposed collagen and continues with the recruitment of additional platelets into a growing mass that will eventually be stabilized with cross-linked fibrin. The intracellular events that support this process are made possible by a "toolkit" of signaling molecules that includes heterotrimeric G proteins, Ras superfamily members, phospholipases that hydrolyze membrane phosphoinositides, lipid kinases that replenish depleted pools of phosphoinositides, protein tyrosine kinases which make possible the formation of massive signaling complexes, and serine/threonine kinases that regulate the activity of other enzymes. Although there is little or nothing in this list that is unique to platelets, collectively these

molecules make it possible for platelets to be rapidly transformed from freely-circulating, non-adherent cells to non-circulating, adherent cells. The rapidity with which this occurs has long made platelets a popular cell for studying signal transduction events.

Formation of a platelet plug can be thought of as occurring in three phases: Initiation, extension and perpetuation (Figure 1). **Initiation** occurs when circulating platelets are activated by exposed collagen and von Willebrand factor, allowing the accumulation of an initial platelet monolayer. Key to this phase of platelet activation is the presence of receptors on the platelet surface that can bind to collagen (integrin $\alpha_2\beta_1$ and GP VI) and von Willebrand factor (GP Ib/IX/V and integrin $\alpha_{IIb}\beta_3$). **Extension** occurs when additional platelets accumulate on the initial monolayer. Key to this phase is the presence on the platelet surface of receptors that can respond rapidly to locally-generated thrombin, secreted ADP and released thromboxane A_2 (TxA_2) to activate phospholipase C, increase the cytosolic Ca^{++} concentration and suppress synthesis of cAMP. Most of these receptors are members of the superfamily of G protein coupled receptors. **Perpetuation** refers to the late events of platelet plug formation, when the intense, but short-lived signals aris-

ing from G protein coupled receptors have faded and the receptors responsible have been desensitized. These late events stabilize the platelet plug and prevent the premature disaggregation that would allow bleeding to resume after initially stopping. Perpetuation is less well understood than initiation and extension, but our recent studies point to a central role for signals generated by a family of receptor tyrosine kinases known as Eph kinases.

Eph kinases, ephrins and the perpetuation of platelet activation. Eph kinases are a large family of cell surface receptor tyrosine kinases whose ligands (known as ephrins) are themselves held to the cell surface by either a GPI anchor (the ephrin A family) or a transmembrane domain (the ephrin B family). The kinases are also divided into two groups (A and B) and, with certain exceptions, the "A" ligands bind promiscuously to the "A" kinases and the "B" ligands bind to the "B" kinases. An exception is EphA4, which turns out to be present on platelets. The EphA4 receptor can bind ligands ephrin B family members as well as ephrin A family members, a point that turned out to be relevant for this story.

Initially identified as orphan receptors, Eph kinases have now been shown to play a critical role in neuronal pat-

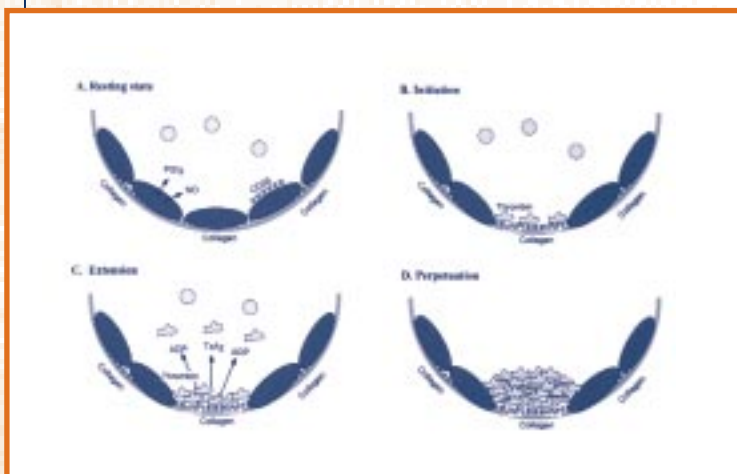
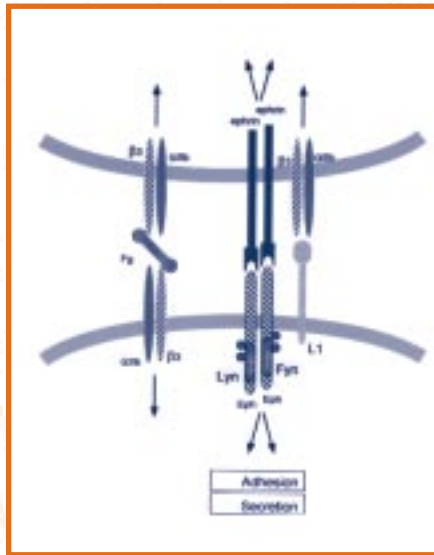


Figure 1. Steps in platelet plug formation. A) Prior to vascular injury, platelets are maintained in the resting state by a combination of inhibitory factors that place a "threshold" that must be surmounted in order for platelets to be activated. These factors include PGI_2 and NO released from endothelial cells, and CD39, an ADPase on the surface of endothelial cells that hydrolyzes any small amounts of ADP that might otherwise cause inappropriate platelet activation. B) The development of the platelet plug is initiated by the exposure of collagen and the local generation of collagen. This causes platelets to adhere and spread on the connective matrix, forming a monolayer. C) Afterwards, the platelet plug is extended as additional platelets are activated via the release or secretion of TxA_2 , ADP and other platelet agonists, most of which are ligands for G protein coupled receptors on the platelet surface. D) Finally, close contacts between platelets in the growing hemostatic plug, along with a fibrin meshwork, help to perpetuate and stabilize the platelet aggregate.

terning and axonal guidance during development. In addition, the expression of Eph kinases and ephrins in the developing vasculature has been shown to be an early marker that differentiates arteries from veins, and interactions between Eph kinases and ephrins are believed to play a critical role in vasculogenesis and angiogenesis. Among other things that activated Eph kinases and ephrins can do is to modulate adhesive interactions involving integrins. That brings us back to platelets. To a large extent, platelets can stick together because their surface is densely populated with an integrin, $\alpha_{IIb}\beta_3$, which on activated platelets acquires the ability to bind plasma fibrinogen – one molecule of fibrinogen binding simultaneously to two different $\alpha_{IIb}\beta_3$ complexes on two different platelets (Figure 2).

The binding of ephrins to Eph receptors causes the clustering of both the ligands and the receptors. This triggers signaling and responses in both the receptor-expressing cells (“forward” signaling) and the ligand-expressing cells (“reverse” signaling) as molecular complexes form around the clustered Eph kinases and ephrins. These events can be dependent on the phosphorylation of the Eph and ephrin, but other protein:protein interaction domains, including PDZ-binding domains, exist in these molecules as well. A large number of signaling molecules have now been shown to associate with Eph kinases and ephrins in cells other than platelets. Most of these molecular interactions require the clustering of the receptors and ligands, but others are constitutive and occur in resting as well as activated cells.

We became interested in Eph kinases and ephrins based on the hypothesis that if they were present on the surface of platelets the ligands and the receptors could become bound to each other once platelet aggregation had occurred. We thought that this would provide a



previously-unrecognized mechanism for contact-dependent signaling within platelets that might contribute to the stability of the platelet plug. Our observations to date suggest that this is, in fact, the case. Based on a combination of western blotting, RT-PCR and fluorescence microscopy, we’ve found that human platelets express two Eph kinases (A4 and B1) and at least one ephrin (B1) that can serve as a ligand for both. Clustering is central to signaling by both Eph kinases and ephrins and we have observed that forced clustering of either the receptors or their ligands causes platelets to adhere to fibrinogen and secrete the contents of their α -granules. To our delight, activation of platelets by a biologically-relevant agonist such as ADP results in the formation of signaling complexes with EphA4 that include two non-receptor tyrosine kinases, Fyn and Lyn, and the cell adhesion molecule, L1 (also known as Ng-CAM). Since L1 can bind to $\alpha_{IIb}\beta_3$, this provides an additional mechanism to reinforce platelet:platelet interactions. Furthermore, interruption of Eph/ephrin interactions in ADP-stimulated platelets studied *ex vivo* has no initial effect on ADP-induced aggregation, but causes the platelets to disaggregate, falling apart prematurely. These results suggest that once sus-

Figure 2. Outside-in and Eph/ephrin signaling help to perpetuate platelet plug formation. Once platelets are activated and incorporated into a growing platelet plug, close cell-to-cell contact appears to make possible additional types of signaling mechanisms. One of these involves outside-in signaling via the $\alpha_{IIb}\beta_3$ integrin. Another involves the formation of macromolecular signaling complexes following the interaction of Eph kinases and ephrins on the platelet surface. These complexes include the Src family members, Lyn and Fyn, and the cell adhesion molecule, L1/Ng-CAM. Others are undoubtedly present as well.

tained contacts mediated by fibrinogen and $\alpha_{IIb}\beta_3$ have occurred, Eph/ephrin interactions, along with outside-in signaling, help to perpetuate platelet aggregation and stabilize the hemostatic plug (Figure 2).

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Skip Brass, M.D., Ph.D., was an undergraduate at Harvard College and received his M.D. and Ph.D. (in Biochemistry) at Case Western Reserve University. After a residency in Internal Medicine, he came to Penn as a fellow in the Hematology-Oncology Division in the Department of Medicine, where he remains as a faculty member. He is currently Professor of Medicine, Pharmacology and Pathology, and he is Director of the M.D.-Ph.D. Combined Degree Program, as well as Associate Director of the Center for Experimental Therapeutics. Current research in his laboratory focuses on the mechanisms of platelet activation.

Platelets: Sticking ...

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Where next? Far from being done, we feel like we have just begun to understand the role of Eph kinases and their ligands in platelet and vascular biology. We don't really understand how the engagement of Eph receptors by ephrins modulates events within activated platelets – or how it fits with other late signaling events during platelet aggregation such as outside-in signaling through integrins. We're just beginning to understand which signaling pathways are involved - and we still haven't proven our central hypothesis, which is that these events really matter. We've just acquired mice with the gene for EphA4 deleted and one of the things that Ryan Fortna plans to do is to see whether platelet plugs are unstable in these mice. He'll do that by following platelet activation in arteries with laser-induced vessel wall injury. In a rotation project this term, Wenying Jian has joined Donna Woulfe to look at the activation of Rap1B in platelets downstream from ephrinB1. Rap1B is a member of the Ras family and is of interest for us because of growing evidence that it participates in pathways that lead to integrin activation. Finally, the expression of Eph kinases and ephrins on cells in and around the vascular space is not limited to platelets. Endothelial cells express these molecules and white blood cells (leukocytes) almost certainly do as well. A reasonable hypothesis is that platelets and leukocytes use Eph kinases and ephrins to talk to each other and to interact with endothelial cells. That remains to be demonstrated.

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Solomon Erulkar Traveling Fellowship

The winner of this year's Solomon Erulkar Traveling Fellowship is Kushol Gupta. Kushol is a thesis student in the laboratory of Dr. Patrick Loll. His thesis research project entails x-ray crystallographic studies of the two active sites of prostaglandin H2 synthase-1 (PGHS).

AWARDS AND HONORS

Richard Assoian, Ph.D., was appointed Associate Editor of *Molecular Biology of the Cell*, effective January, 2002.

Judy Meinkoth, Ph.D. was appointed to the Editorial Board of *Molecular Endocrinology*, as of January, 2002.

NEW PERSONNEL

The Assoian lab welcomes two new members. **Eric Klein**, a graduate student in Pharmacological Sciences, has joined the lab for his dissertation research. **Hanqin Lei** has joined the lab as a research specialist.

Jianuo Liu, M.D., Ph.D., has joined Dr. Song's laboratory where she is studying the role of complement regulatory proteins CD55 and CD59 in vascular and autoimmune disease. Dr. Liu most recently held the position of Postdoctoral Research Associate in Molecular Biology and Immunology at the University of Nebraska.



7th Annual Dolan Boyd Pritchett Memorial Lecture

Circadian Timing in Mammals

Steven M. Reppert, M.D.

Professor & Chair, Department of Neurobiology

University of Massachusetts Medical School

2:00-3:00 p.m., Thursday, March 7, 2002

Austrian Auditorium, CRB

2002 Lambertsen Lecture

Myocardial Regeneration and Heart Failure

Piero Anversa, M.D.

Professor, Department of Medicine

New York Medical College

4:00-5:00 p.m., Thursday, March 21, 2002

Austrian Auditorium, CRB



27th Annual Carl F. Schmidt Honorary Lecture

Beta-Arrestins: Traffic Cops of Seven Transmembrane Receptor Signaling

Robert J. Lefkowitz, M.D.

James B. Duke Professor of Medicine

Duke University Medical Center

4:00-5:00 p.m., Monday, April 8, 2002

Auditorium, Ground Level, BRB II/III

Deaths

It is with deep regret that the Department of Pharmacology announces the untimely death of Dr. Gary Luthin, a former post-doctoral scientist in the department. Memorial inquiries should be directed to Dr. Boris Tabakoff, Dept of Pharmacology, University of Colorado Health Sciences Center, 4200 E. Ninth Avenue, Denver, CO 80262.

Chairman's Corner

"a television is just a small transparent window in the pipe of a spiritual garbage chute."

Victor Pelevin
Bhudda's Little Finger

Communication and transparency are key to effective leadership. We have entered a period of strategic review of programs and structures within the School of Medicine. The Dean and Executive Vice President, Dr. Rubenstein, has been careful to cast a broad swathe over issues for consideration. We have been encouraged to identify particularly factors which will foster excellence. Clearly, the quality of our environment, the need to reinstitute recruitment and the further development of our established programs demand attention in Pharmacology. A striking feature of this process has been the clear articulation of institutional objective and the multiple and diversified efforts to engage the faculty as a whole in such a critical process. The emphases on inclusion and continuous communication (www.med.upenn.edu/penn/strategy/) auger well for the process as a whole. I encourage you all to participate.

While these events are in train, life continues. We were honored by Steve Reppert and Piero Anversa who gave the Pritchett and Lambertsen lectures, respectively; we anticipate keenly the Schmidt lecture due to be delivered by Robert Lefkowitz on April 8th. We congratulate particularly Kushol Gupta; the winner of this year's Erulkar Traveling Fellowship and lament the passing of Gary Luthin, a former post-doc within the Department. While our Graduate Group grows steadily stronger and the quality of journals in which we publish improves, our NIH ranking slipped a few notches this year from 4th to 7th. Although this is an imperfect measurement of achievement, it serves to emphasize the need to infuse our programs with the breath of renewal. Meantime, we celebrate new grants awarded, particularly to young faculty. Amongst these are additional ROIs gained by Wenchao Song

and Steve Thomas and a first by Emer Smyth. These achievements and others, including two pending multi-investigator awards, suggest that we will ascend the tightly grouped Pharmacology rankings next year.

Last week, I had the chance to contemplate the irony of communication thru the medium of TV. The nature of this medium is, indeed, the message. Never more facile, never more distilled the information transferred. Despite my 'flu shot, I shared the syndrome in time, but not space, with Slobodan Milosevic. Flat on my back, I medicated with decongestants, antipyretics and TV. A captive audience; just like Slob. The relative merits of Letterman and Rather, of revealed paternity, of Oscars, Ovitz and oxters dominate visual time, but are not issues of substance. Perhaps the trivialization of brutal reality and hope can afford a breath of distraction. However, when life and death impinge on TV, they are transient imposters, cameo comedians on the authentic Oscar's "thin line which separates tragedy from farce". How contrasting the presentation of Jerusalem on MSNBC and BBC; imagine the further migration from received truth in Paris, Lima or Luanda. Perhaps there is no objective truth or it is too unpalatable to receive. Yet, understanding the other is as necessary to confront as it is to heal.

What little we know of reality, despite satellite phones, 24 hour news, the web, the fractured screens with triple messages, the overwhelming, continuous access. The protagonist in Alan Lightman's brilliant book, "The Diagnosis", suddenly forgets who he is and where he is going; all he can remember is the motto of his company – "The maximum information in the minimum time". Our reality has evolved to the counterpoint. What do we know of the struggle in Afghanistan, never mind the Yemen,

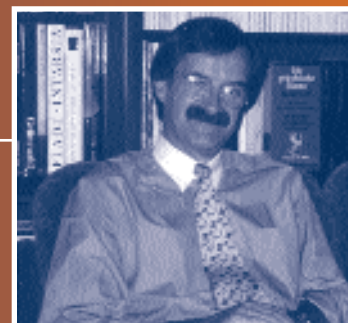
Somalia, the Philippines or the Panski Gorge, despite all the TV time given to the War on Terrorism? The minimum information in the maximum time.

A harsh and enlightening contrast to this predigested pablum was the remarkable video of firefighters rushing to the World Trade Center on September 11th, made by two French brothers. Although sanitized and delayed, its veracity conveyed the horror of the day with a faithfulness to those that perished. The spare elegance of the work's testimony to character, courage, loyalty and faith express the power and beauty of the medium in reflecting the human condition.

Dealing in truth is painful; all the more so when delayed. Defensive prelates in denial joust with celebrity historians at the well of deceit. Reputations crumble as the denouement of Andersen and Enron vie with anniversary of Whitewater to prompt reflection on the ambiguous outcomes of revealed truth. Even biomedical institutions were lately unspared. Drugs and dollars at M.D. Anderson, sex and alcohol at the Rockefeller, McDonalds and Faustian bargains at CHOP. Yet despite the discomfort, the banality, the grim tawdriness of the process, one need only turn back to Milosevic to see the need to deal in reality, to rend the tissue of lies and to permit the inexorable process of the law. Enhancing the freedom of our media and challenging them to communicate substance and diversity of interpretation would seem as fundamental to our individual rights as to homeland defense.

"The stiff spokes of this wheel touch the sore spots of this earth"

Robert Lowell
July in Washington



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