**Sergei A. Grando, M.D., Ph.D., D.Sci.**

**BIOGRAPHY**

***Memberships***

American Academy of Dermatology
Society for Investigative Dermatology
International Society of Dermatology
Dermatology Foundation (Leaders Society)
Medical Dermatology Society
Ukrainian Medical Association of North America
Ukrainian Association of Dermatologists, Venereologists, Cosmetologists

***Professional Background***

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| 2007 - Present | Professor | University of California, Irvine |
| 1996 - 2007 | Professor | University of California, Davis |
| 1991 - 1996 | Associate Professor | University of Minnesota |
| 1990 - 1991 | Acting Professor | Post Graduate Institute for Physicians, Kiev, Ukraine |
| 1985 - 1990 | Assistant Professor | Post Graduate Institute for Physicians, Kiev, Ukraine |
| 1980 - 1984 | Resident/Fellow in Dermatology | Post Graduate Institute for Physicians, Kiev, Ukraine |

***Professional Degrees***

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| 1989 | D.Sci. (Doctor of Science in Medicine) | Central Institute of Dermatology and Venereology, Moscow, Russia |
| 1984 | PhD | Post Graduate Institute for Physicians, Kiev, Ukraine |
| 1980 | MD | Medical Institute, Kiev, Ukraine |

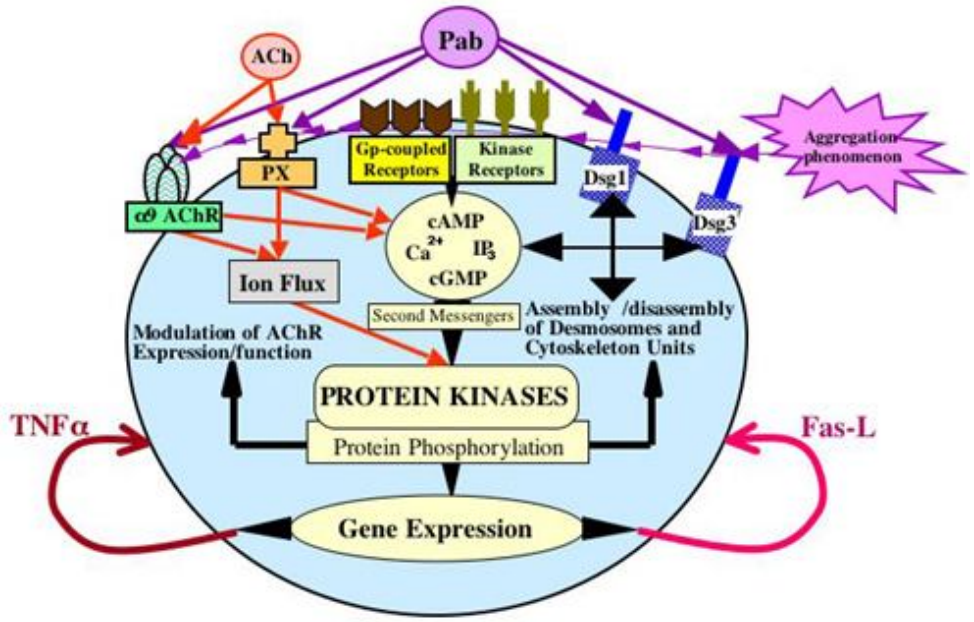
**RESEARCH INTERESTS**

- Immunopathophysiology and non-steroidal treatment of pemphigus
- Cholinergic regulation of keratinocyte adhesion and migration
- Cholinergic effects of tobacco products in non-neuronal tissues

**Immunopathophysiology and development of non-steroidal treatment of pemphigus**

Dr. Grando utilized pemphigus patients' IgGs as a probe to identify the pathophysiologically relevant target antigens in the autoimmune blistering disease pemphigus. He found, unexpectedly, that autoantibodies targeted several known as well as novel members of the acetylcholine (ACh) receptor gene superfamilies expressed by skin cells. Later, he has now demonstrated that these receptors control cell shape and intercellular adhesion, and their blockade by auto-antibodies produces cell dysadhesion and blisters. Dr. Grando's lab demonstrated that pemphigus vulgaris IgG and methylprednisolone exhibit reciprocal effects on keratinocyte adhesion molecules. He discovered novel mechanisms of targeting cell death and survival and therapeutic action of intravenous IgG (IVIg) in pemphigus. The results indicate that in different pemphigus patients, IgG-induced acantholysis proceeds predominantly via distinct, yet complementary, pathways of programmed cell death and that IVIg protect target cells by up-regulating endogenous caspase and calpain inhibitors.

Grando's work in autoimmune pemphigus and paraneoplastic pemphigus has led to the development of non-steroidal therapy for pemphigus and other diseases associated with blistering. He has conducted an IRB-approved clinical trial using a well-tolerated acetylcholinesterase inhibitor, Mestinon, in the treatment of pemphigus patients. The results of his work have altered the way physicians throughout the world understand the mechanisms of pemphigus, and have led directly to the development of new treatment of pemphigus with cholinergic agonist, such as topical application of pilocarpine.

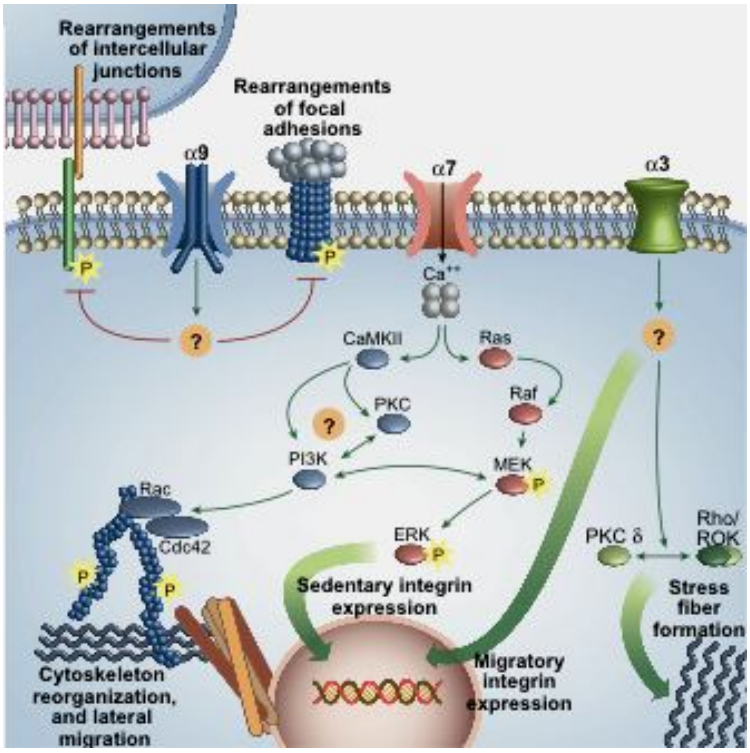



**Immunopharmacology of Pemphigus.** This diagram depicts hypothetical intracellular biochemical mechanisms mediating the synergistic acantholytic effects of pemphigus antibodies and pro-inflammatory/apoptotic cytokines, as well as the anti-acantholytic action of acetylcholine.

Abbreviations: ACh, acetylcholine; AChR, acetylcholine receptor; Dsg, desmoglein; Fas-L, Fas-ligand; IP3, inositol triphosphate; Pab, pemphigus antibodies; PX,

**Keratinocyte adhesion and migration**

The mechanisms mediating and regulating assembly and disassembly of intercellular and cell-substrate junctions is a subject of intensive research. Although functional components of adhesion complexes are well known, much less is known about the signaling mechanisms that initiate, sustain and terminate adhesion and migration. Dr. Grando's research is focused on autocrine/paracrine signaling pathways regulating assembly and disassembly of cell-cell and cell-substrate adhesion complexes in keratinocytes. He has discovered that free cytotransmitter ACh is present in physiologically-relevant concentrations in the



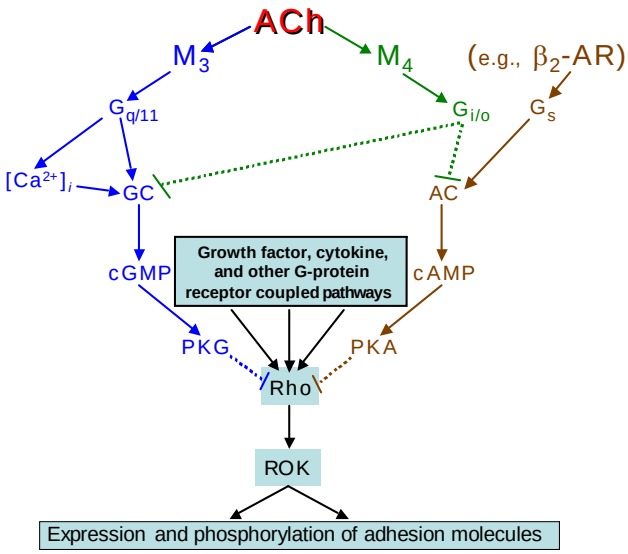

**Nicotinic control of cell adhesion and motility.**

skin. Keratinocytes express both the ACh synthesizing and the degrading enzymes, and there is an upward concentration gradient of free ACh in human epidermis. The repertoire of cholinergic enzymes and receptors changes with cell maturation, so that at each stage of their development, keratinocytess respond to ACh *via* different combinations of nicotinic (nAChRs) and muscarinic (mAChRs) ACh receptors.

Keratinocytes can be simultaneously stimulated through two distinct types of cholinergic signaling pathways: 1) the ionic events, generated by opening of ACh-gated ion channels represented by nAChRs; and 2) the metabolic events, elicited due to ACh binding to the G protein-coupled single-subunit transmembrane glycoproteins, or mAChRs. This diversity could allow the single cytotransmitter ACh to exert diverse effects on keratinocytes at various stages of their development, which helps explain a plethora of biological effects of ACh on keratinocytes.

Dr. Grando's lab showed that endogenously produced and secreted ACh is essential for maintenance of polygonal cell shape and intercellular junctions by keratinocytes, and that individual subtypes of ACh receptors expressed in these cells produce distinct effects on the adhesive function. Treatment with cholinergic-receptor subtype-preferring drugs, transfection with selective antisense oligonucleotides or small interfering RNA as well as null mutations of the receptor genes led to marked perturbations of cell phenotype and functions maintaining epithelial integrity. Apparently, the regulation of cell adhesion and motility by ACh is more complex then it was originally thought, as it involves multiple signaling pathways downstream of the cholinergic receptor subtypes expressed by the cells. These receptor regulate expression and function of adhesion molecules *via* signaling pathways involving both kinases and phosphatases.

Dr. Grando's research has demonstrated that random migration (chemokinesis) of keratinocytes elicited by nicotinic agonists was predominantly mediated by the signaling events downstream of $\alpha 3\beta 2$ nAChRs that involved protein kinase C (PKC)-$\delta$ and the Rho/Rho-associated protein kinase (ROK) pathway. The $\alpha 7$-made nAChR inhibited random migration but facilitated directional migration (chemotaxis). The chemotactic effect of the $\alpha 7$ agonist choline was regulated *via* the




**Muscarinic control of cell adhesion and motility.**
The signaling cascades originating at $M_3$ and $M_4$ include distinct stimulatory (→) and inhibitory (•••|) steps and converge at the common effector pathway involving Rho proteins.

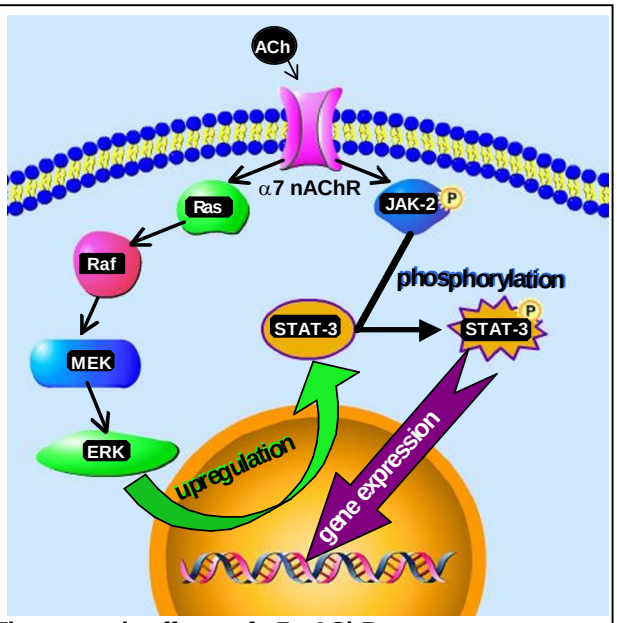
Abbreviations: AC, adenylyl cyclase; AR, adrenergic receptor; $[Ca^{2+}]i$, intracellular free calcium; cAMP, cyclic AMP; cGMP, cyclic GMP; GC, guanylyl cyclase; PKA, protein kinase A; PKG, protein kinase G; ROK, Rho-associated protein kinase.

$Ca^{2+}$-dependent pathway involving $Ca^{2+}$/calmodulin-dependent protein kinase II (CaMKII), phosphatidylinositol-3-kinase (PI3K) and conventional isoforms of PKC, as well as Rac and Cdc42. New data obtained in Dr. Grando's lab implicated engagement of the Ras/Raf-1/MEK1/ERK pathway in mediating the $\alpha$7 AChR effects.

Dr. Grando's lab also has demonstrated that ACh stimulated keratinocyte chemokinesis through the muscarinic pathway *via* $M_4$ mAChR, and inhibited it through $M_3$ mAChR. The $M_4$ effects resulted from inhibition of the inhibitory pathway adenylyl cyclase/cAMP/protein kinase A. The $M_3$ effects were mediated through the intracellular $Ca^{2+}$-dependent guanylyl cyclase/cGMP/protein kinase G signaling upstream from the Rho/ROK pathway. The opposing mechanistic effects of $M_3$ and $M_4$ were accompanied by their reciprocal actions on the expression levels of specific integrin receptors.

**Cholinergic effects of tobacco products in non-neuronal tissues**

Dr. Grando's research has demonstrated that in addition to a well-formulated role of nAChRs in the etiology of addiction to tobacco products, tobacco contributes directly to the tumorigenesis through stimulation of nAChRs in target epithelial cells. His lab has shown that nAChRs can mediate pathobiologic effects of the tobacco and nicotine derivatives on oral keratinocytes. The nitrosamines, just like nicotine, bind to nAChRs and evoke an agonistic response upregulating cell growth. Dr. Grando's research with oral keratinocytes has demonstrated that chronic stimulation of nAChRs with pure nicotine, smokeless tobacco or environmental tobacco smoke can alter normal expression of the ACh receptor genes, providing a positive feedback loop that may lead to aberrant cellular responses to autocrine and paracrine ACh. An increased risk to develop lung as well as head and neck cancers immediately after smoking cessation may, therefore, be related to alterations in the nAChR repertoire in target cells.



**The genomic effects of $\alpha$7 nAChR.**

Carcinogenic nitrosamines activating specific nAChRs may also play a key role in the pathogenesis of cancer by acting as tumor promoters that facilitate the outgrowth of cells with genetic damage (epigenetic effect). This makes pharmacologic modulation of cellular nAChRs a potentially powerful treatment tool for medical conditions caused by tobacco usage.

Current goal of Dr. Grando's studies is to integrate structural and functional information about the molecular aspects of ligation of keratinocyte nAChRs by nicotinergic ligands with the knowledge on the cholinergic pathways regulating acquisition and maintenance of the specific cell state by human keratinocytes.

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