Welcome to the New Journal!

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PubMed search reveals that there are at least 20 scientific journals with the word "Pharmacology" and >10 with the word "Toxicology" in their name. Thus, the first question one needs to ask, what is the reason for launching yet another one, E-Cronicon journal *EC Pharmacology and Toxicology*? One can immediately come up with several answers. First, the field of pharmacology is experiencing an expansion. Second, the development of new tools and approaches led to a paradigm shift in pharmacology. Third, the speed of publication is becoming increasingly important. Last, but not least, the ability of researchers around the world to access published work, guaranteed by open access format, is the key to rapid dissemination of critical findings. Below we will address each of these reasons in a bit more detail.

Expansion of Pharmacology

New classes of drugs are being developed along with conventional ones. For example, G protein-coupled receptors (GPCRs) are now targeted not only by orthosteric ligands (that bind where the natural ligand does), which can be activators (agonists), neutral antagonists, which bind at the same site and competes with other ligands, but do not affect receptor activity per se, and inverse agonists, which suppress basal receptor activity [1]. All of these types of drugs are used, and all of them have one common drawback: they bind and do their thing regardless of the physiological state of the body. A new class of drugs is being actively developed, allosteric ligands, which bind elsewhere in the receptor molecule. Allosteric modulators overcome an important problem of orthosteric drugs: they bind at different sites than conventional ligands, have little to no effect by themselves, but enhance (positive modulators) or suppress (negative modulators) the action of endogenous agonists [2,3], i.e., their action depends on the state of the system. In addition, the realization that GPCRs signal not only via G proteins, but also via bound arrestins, led to the development of biased ligands, which activate one signaling branch, but not the other [4,5]. New small molecule drugs of all these classes are introduced, and relevant information is growing exponentially.

Paradigm Shift: New Tools and Approaches

Small molecules, which are predominantly used as therapeutic tools, have their inherent limitations [6]. Binding affinity is directly related to the energy of interaction: $\Delta G° = -RT ln KA$, where $\Delta G°$ is free energy of association, R is gas constant (1.99 cal/mol x deg), T-temperature in degrees Kelvin, and K_A-equilibrium association constant. Due to its size and consequent small number of interacting elements small molecule can only bind with reasonably high affinity in deep pockets of proteins. This explains why only a small fraction of proteins, ~400, or < 2% of the total number encoded by human genome, is targeted today, and no more than 10-14% of proteins are considered druggable [7]. This also explains why receptors and enzymes are the most common drug targets - both types of proteins have deep pockets that can be targeted by small molecules with sufficient affinity and specificity to achieve therapeutic effect. Any non-substrate molecule binding in the active site of an enzyme or a transporter would act as an inhibitor [1]. Whereas receptors, including GPCRs, offer greater variety of choices, certain limitations associated with relatively small size of conventional therapeutic agents remain.

Protein-protein interactions, which mediate many critical signaling events in the cell, are usually mediated by unstructured elements or flat surfaces, neither of which can bind small molecules with high affinity. Moreover, protein-protein interactions often involve large surfaces (> 2,000 Å [2,8]), and therefore are unlikely to be significantly affected by a small molecule. In a few cases when protein-protein interactions were targeted, the molecules were designed to disrupt them, even though strengthening certain interactions might be desirable [9]. These are the reasons why several alternatives to small molecules are being developed or proposed for therapeutic purposes.

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Historically, antibodies were the first type of non-small molecule therapeutics [1]. The key limitation of their use is that antibodies can bind extracellular targets, whereas most regulatory signaling circuits, including those implicated in numerous disorders, and are inside the cell. Several new tools that have a potential to revolutionized pharmacology have recently appeared. As we discussed them in detail recently [10], here we will only briefly mention them.

Inherited disorders caused by mutations in various proteins, including GPCRs [11,12], are the hardest to treat. Three different tools for genome editing, which can address the root cause of these problems, have been developed [13]: zinc finger nucleases [14], TALENs [15], and CRISPR-Cas system [16-18]. These tools can be used to correct genetic errors and/or change expressed proteins in the desired direction. Most congenital and acquired diseases are associated with faulty signaling. Proteins are the ultimate signaling tools, with built-in advantage of being sensitive to the regulatory inputs from the cell [6]. However, most proteins have numerous functions, which complicates comprehensive understanding of their biology and their use as therapeutic tools [19]. Even proteins in the visual signaling cascade that were long regarded as ultimate "one-trick ponies" are discovered to have many unexpected functions [20-22]. Luckily, expanding understanding of structural basis of different functions of at least some regulatory proteins, such as arrestins and GRKs [19,23,24], enables the construction of mutants with defined functional characteristics. These mutants can be used to rebalance cell signaling compensating for mutations in other proteins [25], or simply channel cell signaling in the desired direction [23]. Simple examples: an input telling the cells to live longer can counteract the opposite message cells receive in neurodegenerative disorders (Alzheimer's, Parkinson's, retinal degenerations), or an input ordering cells to stop proliferating can solve the problem of cancer. Naturally, the use of all genome editing systems and proteins as therapeutic tools is gene therapy: it requires the delivery of coding sequences to targeted cells under promoters that will drive protein expression. Various methods of delivery of coding DNAs, both viral and non-viral [26-27], are being rapidly perfected. Several clinical trials show that gene therapy is coming of age and is ready for wider use [28].

Yet another proposed alternative to conventional small molecules is therapeutic use of living cells [29]. While the safety of the use of self-replicating therapeutic agents, such as cells, is debated [10], we should not reject any potential avenues offhand. Thus, it is obvious that inherent limitations of the therapeutic potential of small molecules are becoming increasingly obvious, and various alternatives with expanded capabilities are being proposed and developed. The toolbox of pharmacology is expanding, and this process must be reported in a timely fashion by scientific journals.

Rapid Publication

There is general tendency for acceleration of peer-review and publication process. Quite a few new journals aiming at quick review and immediate on-line publication of accepted papers in the fields of pharmacology have been started recently. *EC Pharmacology and Toxicology* certainly aims to fill this niche.

Open Access

Publication makes most sense when published papers immediately become available to the widest possible readership. Open access format was developed to achieve just that. *EC Pharmacology and Toxicology* is not the only open access journal in the field, but it is launched in this format to achieve speedy wide dissemination of published material.

To summarize, *EC Pharmacology and Toxicology* is launched at a time of expansion of traditional and innovative pharmacology and toxicology and it offers rigorous peer review, rapid publication of accepted papers, and wide dissemination of the results due to open access. These are the reasons for its creation, as well as the reasons to publish high quality science in this journal.

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