Published in final edited form as:

Expert Opin Ther Pat. 2015 January ; 25(1): 125–129. doi:10.1517/13543776.2015.993539.

A Key Opinion Leader interview: insight into the research and career of Dr KA Jacobson

Claudia Palmer [Commissioning Editor]

Welcome to the first Key Opinion Leader interview for Expert Opinion on Therapeutic Patents. Today, I am talking with Professor Kenneth A. Jacobson, who is an esteemed member of our editorial board.

Introduction

Kenneth A. Jacobson, Ph.D. is Chief of the Laboratory of Bioorganic Chemistry and the Molecular Recognition Section at the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health in Bethesda, Maryland, USA. Dr. Jacobson is a medicinal chemist with interests in the structure and pharmacology of G protein-coupled receptors, in particular receptors for adenosine and for purine and pyrimidine nucleotides. He graduated from Reed College, Portland, Oregon, with a B. A. in Liberal Arts, but majoring in chemistry. He received his Ph.D. in Chemistry at the University of California San Diego and was a Bantrell Fellow at Weizmann Institute of Science in Israel before joining the NIH. Recent awards include 2014 Highly Cited Researcher in Pharmacology and Toxicology by Thomson Reuters, the 2003 Hillebrand Prize of the Chemical Society of Washington for original contributions to the science of chemistry, the 2009 Pharmacia-ASPET Award in Experimental Therapeutics, 2009 Sato Award, and the 2014 Goodman and Gilman Award in Receptor Pharmacology. Dr. Jacobson has served as Chair of the Medicinal Chemistry Division of the American Chemical Society and was inducted into the Division's Hall of Fame in 2009.

1. Your research focuses on the structure and pharmacology of G protein-coupled receptors (GPCRs), what led you into this area of research and what interests you most about it?

I began with the study of beta-adrenergic receptor ligands in graduate school. The idea was to couple the agonist isoproterenol covalently and irreversibly to peptide carriers and thereby alter the pharmacological profile. The medicinal chemistry of the biogenic amines at their GPCRs was attractive to study because the beta-adrenergic receptor was one of the few cases of a GPCR, at the time, which showed a clear division of receptor subtypes and correlation with molecular structure of the

Declaration of interest: K Jacobson has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Disclaimer: The opinions expressed in this interview are those of the Interviewee and do not necessarily reflect the views of the Expert Collection.

ligand. We found that the potency could be greatly enhanced by large pendant groups, implying that the receptor binding site had an outer region open to the extracellular milieu, as well as an inner region that was less tolerant of major changes. This was before we had any knowledge of the receptor's structure, before the first cloning of a GPCR (other than rhodopsin), so the concept of a receptor was more theoretical than actual. Now we know that the GPCRs are the largest single class of signalling proteins in the human genome and remain one of the most fruitful areas of pharmaceutical discovery

The adenosine receptors and P2Y receptors have not yet led to nearly as many drugs as the biogenic amine receptors. In fact, there are very few. However, these receptors, in particular, are unusual in their involvement in every tissue and physiological system, and it's hard to identify a disease that does not have some connection to at least one of these 12 receptor subtypes. Extracellular nucleosides and nucleotides have been around as endogenous protective agents in the body throughout most of evolution. Thus, any medicine we can design to modulate this biological control system, based on purine receptors, is actually mimicking and improving upon a natural protective process. And, we know that nucleosides tend to make good drugs, in general, with dozens that act through other pathways approved for therapeutics.

2. Are there any particular people that have been an influence in your career?

My interest in chemistry began in grade school – chemistry was already a family tradition. My grandfather Abner Jacobson who studied chemical engineering was from a Latvian-Jewish immigrant family in Cleveland, Ohio and became an inventor. He was the youngest child and first in his family to attend college, and his education was financed by his siblings. Among his accomplishments: when the supply of dyestuffs from Germany was cut off in World War I, was the first to devise a process to synthesize and manufacture navy blue dye in the U.S. He introduced me to viewing the world at the atomistic level and to chemical transformations, which I practiced in my basement chemistry lab as a kid. As an 11-yr. old, I wrote to chemical companies asking for samples of organic dyes for a science project, which they readily sent me. I collected several dozen and drew their structures. My chemical hobby almost ended when I accidentally turned my eye orange while trying to do a reaction on fluorescein dye.

My Ph.D. advisor Murray Goodman made me aware of the power of interdisciplinary science and the need for an effective researcher to build an organization. He was an organic chemist but with broad interests, contributing to the structure, computer modelling, synthesis and biology of peptides. When I started my lab at NIH, the first postdoctoral fellow I hired was a pharmacologist to characterize the ligands that I was synthesizing, following in the Goodman model. Also, my interest in functionalization of small molecules for covalent attachment to larger carrier moieties, in a way that preserves or enhances the pharmacological profile began in Goodman's lab. This has led, for example, to our fluorescent probes of GPCRs and dendrimer conjugates.¹

Abraham Patchornik at Weizmann Inst. challenged me to be more creative in thinking about design and functionality of biomolecules. For example, the interaction of biomolecules with light to initiate protein labelling, regeneration reactions and thinking about multiphase systems. A number of times, at the end of a week of hard work, he parted with the “assignment” that I should come back to the lab the following week having in mind a “new concept in chemistry”. I was introduced to nucleotide chemistry at Weizmann. We were working on new polymeric reagents for oligonucleotide synthesis. So, when I later arrived at NIH in a second postdoctoral position, I already was familiar with their chemistry, but not yet the role of extracellular nucleosides and nucleotides in cellular signalling.

Finally, collaborating with John W. Daly at NIH for most of my time here at NIH opened the depth and diversity of biological molecules, their structure activity relationships and signalling pathways. Daly was a pioneer in adenosine receptor pharmacology and the search for selective ligands. He also studied synthetic chemistry in graduate school and learned pharmacology after coming to NIH, from none other than from Julius Axelrod. Fortunately, the local environment in the NIH lab I joined was very supportive and encouraged exploration of original ideas. So, I was following in a fine scientific tradition in a lab that encouraged collaboration between chemists and biologists.

3. What has been the biggest success of your career?

Training many junior researchers, including over 70 postdoctoral fellows, and watching them succeed in their own careers have been gratifying. On the technical side, I have carried through my career and developed specific major research themes and long-term goals or visions. The ability to “see” receptors in 3D and to manipulate their ligands accordingly is one goal that is now coming to fruition. When I first came to NIH and started drawing little cartoons of receptors to explain why I was derivatizing theophylline, for example, in a particular manner, I was ridiculed by certain traditionally-thinking researchers. At one point I was even told that I “didn’t have enough respect for the molecules”. Some of the pharmacological probes we introduced were even called “Baroque” because they seemed to be more decorated than was necessary. Now it seems obvious why I persisted in attaching chemically functionalized chains on these molecules to make new tools to understand their interaction with the receptors.

The spectacular GPCR structures that we have now completely change the thinking in the field. This advance is certainly thanks to the Nobel Prize work of Brian Kobilka and Robert Lefkowitz, and also to many others, notably Ray Stevens who has been very active recently in elucidating many new GPCR structures. Thus, using structural knowledge to guide ligand design is becoming a major success route in medicinal chemistry.

Our lab is privileged to collaborate on the determination of various purine receptor structures with Ray Stevens and his colleagues Qiang Zhao and Beili Wu who have opened their own lab at the Shanghai Inst. Materia Medica. We have already reported on the structures of an agonist-bound A_{2A} adenosine receptor that is a

target of Parkinson's disease and both agonist- and antagonist-bound P2Y₁₂ receptors. The P2Y₁₂ receptor is a target of antithrombotic drugs, including the blockbuster Plavix and newer antagonists. In the medicinal chemistry of the members of these receptor families, using both empirical and structure-based design processes, we have introduced key pharmacological tools that have enabled progress in research on adenosine receptors and P2Y receptors. We introduced over 35 compounds that are used widely in this field, both as potential therapeutic agents and as compounds for proof of concept, and most are currently available from commercial sources. I enjoy learning about the actions of our compounds by reading the literature. These compounds have been very useful if not essential for defining many new therapeutic concepts based on selective GPCR ligands. Of course, the translational implications for two A₃ agonists invented in our lab for the treatment of autoimmune inflammatory diseases and cancer are very promising. We are fortunate that the private sector has licensed these nucleoside derivatives and is advancing them in clinical trials. There are other examples of probes from our lab that pointed the way for other pharma companies to design their own clinical candidates.

4. To what do you attribute your success? And what motivates you in your career?

I have been fortunate to have many dedicated and gifted co-workers and collaborators. My work is largely curiosity-driven. Our introduction of key pharmacological probes for adenosine was initially motivated by the desire to use chemistry to complement a biological research need. Now it is apparent that some of these compound classes have translational potential, so the thought of making a molecule that will benefit patients is a driving factor. As a chemist, to see two of the molecules envisioned and first synthesized in our lab being administered to >1200 people in clinical trials – and moreover found to be free of serious adverse effects – is very satisfying.

5. During your career as a medicinal chemist what technologies have been developed that have been invaluable to your research?

I have been in the field long enough to recall, as a young student, the introduction of radioligand binding technology for opioid receptors by Sol Snyder and others. This has been the most important single (easily accessible) technique that has allowed us to progress in developing purine receptor ligands. Now, fluorescent techniques, such as high affinity GPCR agonists and antagonists that contain fluorophores, are promising for drug discovery. The ability to crystallize GPCRs for X-ray structural determination has been of tremendous benefit in shifting to rational drug design from the purely empirical and more labour-intensive approach.

Another technique that I have benefited from is library screening to discover new chemotypes to interact with particular receptors. Now, the standard is to use in silico screening for novel ligands of GPCRs that have either X-ray structures or homology models based on closely related X-ray structures. It's amusing that my first chemical library in the mid-1990s was assembled from collecting research and commercial samples from various sources. This was before we could readily access

an existing chemically diverse library. I climbed up to high shelves in NIH chemistry labs, where samples from past decades were stored; selecting bottles that I had a hunch might be adenosine antagonists. A modest-sized hand-picked library enabled us to identify the first antagonists of the A₃ adenosine receptor, which were then chemically optimized by exploring the structure activity relationships. What turned out to be one of the best leads, a pyridine derivative, was prepared by Bernhard Witkop and dated 1953.

6. As an Inventor of 34 patents, what challenges do medicinal chemists face when patenting molecules?

Patenting is a financial commitment with filing and prosecution costs that increase over time before the patent is granted. There is also a time commitment to ensure that the drafted application and claims adequately describe the subject molecules and their use. The decision to patent within the academic environment must be made before publication. At that time there usually has not been translation of these inventions to full use in the clinic. The pharmaceutical industry is interested in licensing technology, i.e. drug candidates, from universities and government labs, but the preference for technologies with demonstrated preclinical utility and safety is difficult to meet. This process of de-risking drug candidate molecules is challenging for the non-pharma scientist who might lack knowledge of the decision criteria and lack funds for adequately advancing the molecules beyond simple cell models and initial in vivo tests.

7. Your recent research involves working to develop more potent and selective human A₃ adenosine receptor (AR) agonist ligands. Explain what you have discovered so far.

I view the ligands of adenosine receptors and P2Y receptors as agents that can modulate an entire biological system at multiple points, which relates to endogenous defence against stress to an organ or tissue. The A₃AR agonists appear to be especially beneficial in many disease models. My NIH team and I introduced the first selective agonists and antagonists for this GPCR in 1993-1996. At first, it was exciting to learn of a newly cloned AR, knowing that the previously discovered A₁ and A_{2A} receptors whose manipulation have protective effects in disease states. In 1992, we had little inkling of what diseases A₃AR agonists or antagonists would be useful in treating. That information became apparent only later, after we and many other labs used our definitive ligands in disease models. A₃AR agonists have anti-ischemic and cytoprotective effects, as we showed from 1994 onward.² In general, A₃AR agonists protect normal cells and do not support harmful cells, like tumor cells. They regulate intracellular pathways to correct imbalances created by the disease state in these signalling pathways that converge on transcription factors. This has been confirmed in the subsequent clinical trials carried out by CanFite Biopharma, a small Israeli biotech that has licensed several of our prototypical A₃AR agonists for treating autoimmune inflammatory diseases and cancer. In cells from rheumatoid arthritis (RA) patients, for example, the A₃AR agonist CF-101 (our designation is IB-MECA) reduces the proinflammatory

cytokine tumor necrosis factor and the transcription factor NF-kappaB, which are known to contribute to the severity of the disease. Moreover, the clinical trials conducted by CanFite detected that the patients with RA or psoriasis who responded positively to the drug in Phase II clinical trials had a higher level of expression of the A₃AR in diseased tissues and in peripheral blood mononuclear cells. This high level of A₃AR in diseased tissue could be measured and used as a biomarker to predict the efficacy of the A₃AR agonist in a given patient. CanFite is also conducting a trial of another related A₃AR agonist, CF102 (our designation CI-IB-MECA) in primary liver cancer with initial encouraging results indicating prolonged survival.

Recently, in collaboration with Daniela Salvemini of St. Louis University we have been looking at the application of A₃AR agonists to treating chronic neuropathic pain.³ This type of pain, which is very common in the population, can result from diabetes, cancer chemotherapy, cancer itself, infection, injury or many other conditions. With respect to pain, the A₃AR had been dismissed prematurely in some earlier review papers as 'causing pain' until Daniela Salvemini generated a huge body of experimental evidence that A₃ agonists reduce chronic pain but not acute pain. We recently published two new papers that reveal the effects of spinal A₃ receptors in preventing and reversing chronic neuropathic pain, and more are in the works on this topic. There are also beneficial supraspinal actions, and even endogenous adenosine has been found to act through the A₃ receptor (as well as the A₁ receptor) to lower chronic pain. A₃ agonists work by a novel mechanism unlike any pain medication on the market, one that is not dependent on opioid or cannabinoid receptors. Recently, we have been working to design highly selective and drug-like A₃ agonists for use in pain control.

8. How much of your work has led to translatability to the clinic?

So far, only two of our A₃AR agonists have entered clinical trials. Twelve clinical trials with our A₃AR agonists are already listed on clinicaltrials.gov with seven recruiting or completed. The compounds have so far been administered to over 1000 people and show signs of efficacy in RA, psoriasis and hepatocellular carcinoma. Other compounds we introduced have inspired and enabled work in pharma that has led to clinical candidates acting through the same mechanism. We are also hopeful that our agonist of an ion channel on heart muscle cells, a P2X₄ receptor (not a GPCR, but still a purine receptor), will move in that direction. There are about six million adults in the US with heart failure, and about half will die within five years. We are collaborating with Dr. Bruce Liang of the University of Connecticut on this project. He has identified compounds that open this channel in the same way as endogenous ATP and that raise localized, intracellular nitric oxide to protect the heart in models of heart failure⁴. Our agonists increase survival in animal models by delaying the progression of heart failure. They reduce cardiac hypertrophy and improve the ability of the myocyte to contract without major changes in Ca²⁺ or cAMP or altering blood pressure and heart rate.

9. What do you predict will happen in G protein-coupled receptor (GPCR) research over the next 5 years?

It will likely become more computationally oriented with many new X-ray structures available. In other words, it will no longer be necessary to screen robotically through large ($>10^6$) chemical libraries; rather, the in silico screening will precede screening at the bench.⁵ Known ligands can also be optimized by tweaking their structure based on the insights from X-ray crystallography, and off-target effects can sometimes also be analysed. Thus, the new GPCR structures and rational design methods will increasingly improve the efficiency of drug discovery. Also, the greater structural insight within this family might help identify endogenous ligands for the numerous orphan GPCRs, of which there are still many. Many non-orphan GPCRs are targeted therapeutically with great success, and it is expected that the hundreds of GPCRs that are not yet associated with any approved pharmaceuticals, including some of the hundreds of olfactory receptors, will provide fertile new areas for drug discovery. GPCRs that assist in viral infection are being examined as possible leads for new anti-infective agents. The future for GPCR research and its continued translation to the clinic remains bright.

Biography

References

1. Jacobson KA. Structure-based approaches to ligands for G-protein-coupled adenosine and P2Y receptors, from small molecules to nanoconjugates. *J Med Chem.* 2013; 56:3749–3767. [PubMed: 23597047]
2. Fishman P, Bar-Yehuda S, Liang BT, Jacobson KA. Pharmacological and therapeutic effects of A₃ adenosine receptor (A₃AR) agonists. *Drug Disc Today.* 2012; 17:359–366. <http://www.ncbi.nlm.nih.gov/pubmed/22033198>.
3. Little JW, Ford A, Symons-Liguori AM, et al. Endogenous adenosine A₃ receptor activation selectively alleviates persistent pain states. *Brain.* 2015; 138:28–35. [PubMed: 25414036]
4. Yang T, Shen JB, Yang R, et al. A Novel cardioprotective role of endogenous cardiac myocyte P2X₄ receptors in heart failure. *Circ Heart Fail.* 2014; 7:510–518. [PubMed: 24622244]
5. Jacobson KA, Costanzi S, Paoletta S. Computational studies to predict or explain GPCR polypharmacology. *Trends Pharmacol Sci.* 2014; 35:658–63. [PubMed: 25458540]