Alfred Goodman Gilman was born in the same year (1941) that his father and Louis Goodman published the first edition of The Pharmacological Basis of Therapeutics. *Pharmacology has thus always been part of his life, and in his own career he has focused primarily on cell signaling. For the past twenty years, he has chaired the Department of Pharmacology at UT Southwestern, and his long list of accomplishments includes a Nobel Prize (1994) for his work on G proteins. In 1998, Gilman embarked on his most ambitious program of research yet, bringing dozens of leading investigators from the cell signaling community to Dallas in order to plan out a ten-year project aiming "to understand as completely as possible the relationships between sets of inputs and outputs in signaling cells." Now directing the full-fledged, federally funded Alliance for Cellular Signaling, Gilman stresses that a solid database for constructing a "virtual cell" will depend on extensive collaboration from the entire signaling community. (For a complete Program Summary, and to register for membership in the Alliance, consult www.cellularsignaling.org.) The luminaries that were invited to the Dallas planning meeting, in fact, were greeted at the door with a note from Gilman exhorting them:*

Please Check EGO at Door.

Alfred Goodman Gilman
University of Texas
Southwestern Medical Center at Dallas

mi: It was sixty years ago today[1] that your father and Louis Goodman penned the preface to the first edition of their textbook (soon to appear in its tenth edition). It thus seems fitting, before we discuss your work with the Alliance, to ask about your first encounter with *The Pharmacological Basis of Therapeutics*. When did you first actually read the book?

AG: Well, I think I helped number the pages for the manuscript for the second edition (1955). It certainly pervaded my family's life. My mother typed the first two editions on a portable Royal typewriter with something like six carbons, which must have been sheer hell. With the third edition in 1965, I actually got copies of the proof from my father to prepare for my qualifying exams. I was an MD-PhD student then.

Reductionism has worked, and it's been fun. But I think for much of my career, I have tried to figure out how we're ever going to close the loop and put all of our wonderful reductionistic information into a bigger context.

mi: If your father hadn't been a pharmacologist, do you think you still would have been drawn to the field?

AG: I tried to avoid pharmacology. I was more attracted to biochemistry, my major as an undergraduate (Yale). And then Earl Sutherland recruited me to the MD-PhD program that he had established in Cleveland. The program was quite revolutionary. Earl recruited everyone in that program. He had identified all of the students in it by some sort of personal contact. His son was in the program. He knew about me via my father; they were friends. Earl invited me out to look at that program and I resisted it for a while because the prospect of spending seven years in Cleveland didn't appeal to me. But finally I did go out and look at it. I said to Earl that I didn't really want to be a pharmacologist. And he just put his arm around me and he said, "It's OK. The kind of pharmacology that we do around here is really biochemistry with a purpose." And that cooked my goose. He had just discovered cyclic AMP and I thought that would be really exciting. And it was.

mi: From Cleveland, you worked your way south to Dallas. What brought you to UT Southwestern?

AG: Well, I would say this school is uniformly excellent now. It wasn't quite that good in 1981 (when I arrived), but there were some enormous strengths, which really started in the Department of Medicine with Donald Seldin. Seldin was the one who really set the intellectual tone here from the very beginning. The Department of Medicine had given birth in essence to Joe Goldstein and Mike Brown (Nobel laureates, 1985) who then moved to form their own department. And there were other very good departments at the time: Microbiology, Cell Biology, and Biochemistry. Pharmacology still had its original Chairman, and he was a very dignified and talented man, Andres Goth, who also wrote a pharmacology textbook. But the school hired me with a mandate to modernize the department. And that attracted me, as did particularly the presence of Goldstein and Brown just down the hall, who are very good friends of mine. And the atmosphere here is really different from most places. We are very collaborative, we are very friendly, and we do not fight over turf. We interact very well. When there are new resources available people get together to try to figure out how to use them optimally, rather than trying to grab on to pieces for themselves.

mi: What do you think accounts, here in Dallas, for the enthusiasm for collaboration and for the resulting strength in research productivity?

AG: Well, if you could figure it out, you could bottle it. But I think there are several things. The administration here is unabashedly ambitious in all the finest ways. They want to be the best there is, and they want to build that on the foundation of being the best research institution. So their support for research is solid and continuous. Both the administration and the leadership of the faculty are very, very strong. People are happy here.

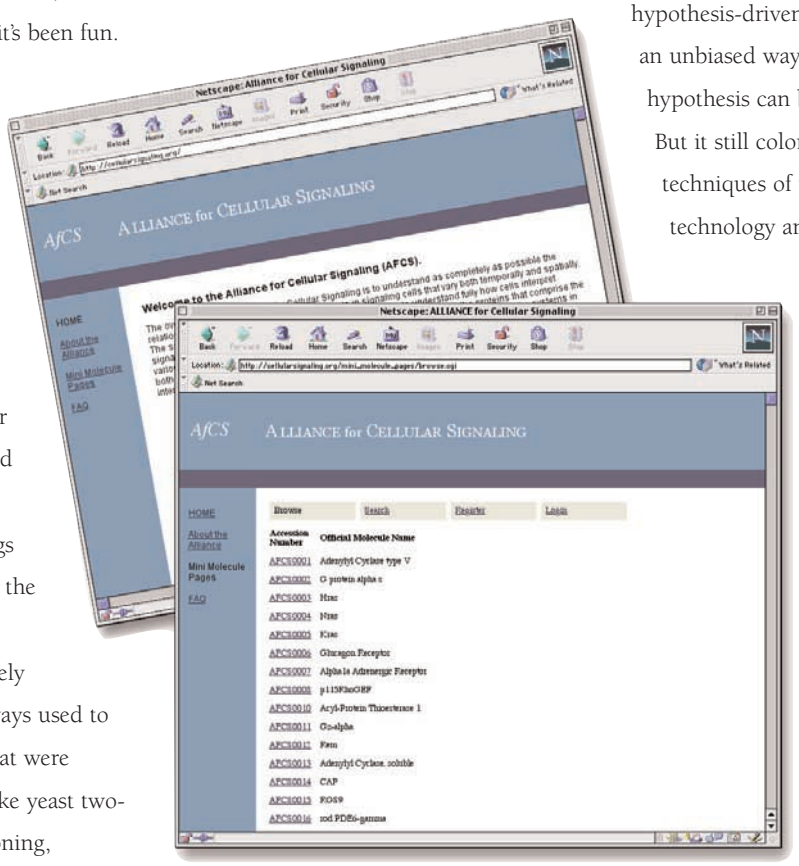
[1] The interview was conducted on November 20, 2000.

...I think now we need to get a bit away from this glorification of hypothesis-driven research. Hypothesis-driven research is quite wonderful, but it's not the only way.

Sometimes we have a little trouble recruiting here because it's Dallas—people think they're going to dry up into dust in the summer. But once people arrive here they usually don't leave. The faculty is very happy and very loyal.

mi: Yours has been the first Glue Grant from the National Institute of General Medical Sciences (NIGMS) to be funded (http://www.nigms.nih.gov/funding/gluegrants.html). How did the Alliance for Cellular Signaling come about?

AG: I start by saying that most people in the world think that I am a reductionist and only a reductionist, but that's not true! Reductionism has worked, and it's been fun. But I think for much of my career, I have tried to figure out how we're ever going to close the loop and put all of our wonderful reductionistic information into a bigger context. Many times the thought crossed my mind, if everyone would just get together to work on one system, we could to a certain extent do a hell of a lot better. And now, lots of things have changed, most particularly the sequencing of the genomes of multiple organisms. That is hugely enabling. In my own lab we always used to avoid the sort of experiments that were purely technologically driven, like yeast two-hybrid screens or expression cloning, because we knew we'd surely get data—we'd get a sequence—but then we would have to spend the next god-knows-how-many years trying to figure out what it meant in terms of cell function. Now, we can use databases to identify such sequences within a functional context. When this type of sequence identification first became possible, that was sort of a defining moment for me. What it really means to me is that you can take nonbiased approaches to research. And I think now we need to get a bit away from this glorification of hypothesis-driven research. Hypothesis-driven research is quite wonderful, but it's not the only way.



mi: Do you find the concept of non-hypothesis-driven research to be met with some skepticism?

AG: Very often. A favorite mantra of grant reviewers is, "We don't perceive a hypothesis." Or, "It's overly ambitious." Or they say, "It's diffuse." I think when reviewers just don't like a grant proposal and they don't know what else to say, one of those three things will be used for cover. But it is true now that you can take approaches that are not biased. And a hypothesis can be looked on in many ways as a bias. Now the idea behind hypothesis-driven research is to decide in an unbiased way of course whether the hypothesis can be supported or not. But it still colors the approach. The techniques of recombinant DNA technology and proteomics, and the complete genome in the computer, allow you to take totally nonbiased approaches.

In terms of objections to the formation of the Alliance specifically, I think that we've had to correct some misconceptions. When I first presented the idea

for the Alliance publicly, I was at a small G protein meeting in New York, predominantly attended by younger people. I was particularly interested in their views. The first thing out of somebody's mouth was, "Oh you megalomaniac, you're just trying to take money away from RO-1s, conquer the world, and leave us all out of the picture..." But that's absolutely not what we're trying to do. We really want to empower people to do more, not less. Whenever we've had the chance to talk to people with concerns, we've been able to correct their misconceptions and change their mind.

mi: So when did the funding opportunity first arise for you to start pursuing "nonbiased" research into cell signaling?

AG: Well, the first specific opportunity was a series of planning meetings put together by NIGMS in 1998. They were looking for suggestions about what sort of programmatic things they might do that would be appropriate in the postgenome era. At the meeting I attended, there were at least three of us who came with the same basic idea. NIGMS kept hearing that researchers wanted a new type of funding mechanism to allow large-scale, broad collaborations to attempt the sort of synthesis that could be undertaken now that genomes were characterized. The NIGMS staff consequently published a Request for Applications for large-scale collaborations which they ended up calling Glue Grants.

We have a lot of people involved in signaling here at UT Southwestern, particularly in this department but also in other departments, and we began a series of local meetings to put a plan together for a Glue Grant to identify all the proteins that contribute to cellular signaling. We then invited roughly thirty to forty people to a two-day meeting that we had here in Dallas. It was a very substantial group from the signaling community. We only gave a few weeks notice before the meeting, but virtually everybody came.

NIGMS kept hearing that researchers wanted a new type of funding mechanism to allow large-scale, broad collaborations to attempt the sort of synthesis that could be undertaken now that genomes were characterized.

mi: And what decisions came out of that early meeting of people from the wider signaling community?

AG: Well, everybody said they would be willing to participate in the Alliance, with a single exception: one individual who said he was "reluctant to get involved with any project where the really big answers won't be known until well after the time of [his] death." Now what's so distressing to me about that statement is that it came from a superb scientist who is: 1) very smart, and 2) fairly young!

But, generally, everyone was very enthusiastic about the prospect of developing a "virtual cell." People started signing up for jobs within the Alliance, and a more concrete result of that first meeting was the decision about the cell types that we would study, namely, the cardiac myocyte and the B lymphocyte, both from mouse.

mi: And why choose two cell types?

AG: One reason is that we didn't have the nerve to pick just one, even though we need to acquire a critical mass of data from one system, prepared as homogeneously and consistently as possible, over a long period of time—that's going to be critical. But we were unable emotionally to put all our eggs in one basket. And three cell types sounded like too many. So it was almost two by default.

Now as soon as the Alliance started to get a little publicity, a couple of people said this is a terrible idea—you can't learn anything by studying just one or two systems. You have to study them all, from different organisms. But I think that those people just absolutely miss the point. If you study everything—well, that's what the world is already doing—then you are prohibited from getting the really detailed information. What the world is doing is a wonderful way to learn the components of signaling systems, and a wonderful way to learn how individual signaling modules work. But it's not a good way to learn how all the modules fit together and how the system functions as a whole. To see how the system functions as a whole, we're going to have to look at the whole system—and that means that we will not restrict ourselves to

signaling involving G proteins—we'll require a huge amount of data focused on all of the cell signaling systems of one or two cell types.

mi: So with respect to perfecting two cell culture systems, you're really going to be offering some new tools to the community. Is that part of the rationale for the Alliance?

AG: Well, we're doing some technology development as necessary, funded as "Bridging Projects" within the Alliance. But that's not our primary business. Our goal is to generate data—to identify the pieces of the cell signaling "puzzle"—and then see how the pieces fit together and how information flows. What we will primarily offer to the community is free access to our data and insights into how signaling systems are built and organized.

mi: Well that brings us really to one of the most intriguing aspects of the Alliance—the fact that all of the Alliance's data...

AG: ...will all be placed directly into the public domain, except for the bridging projects where our investigators develop new technologies. But for the most part we'll do experiments to identify pieces of the "cell signaling puzzle," and if the results satisfy pre-defined statistical criteria of reliability, then the data will automatically be placed in the public domain on the Internet. The simplest example is our screens to detect protein-protein interactions, be they yeast two-hybrid screens, or coimmunoprecipitations, or others. We'll be very good at generating such data.

But each hit in a screen has to be validated as to whether it's real, physically, and whether it is important, physiologically. And we don't begin to have the manpower or the talent to do that. And so we need to enlist the whole signaling research community to be aware of what's going on in the Alliance, to look at our Web site, to see what's happened with their favorite molecules and to follow up on those leads. We totally appreciate that researchers in the signaling community at large will follow up on the leads that we provide only if they are assured of a level playing field. And we in the Alliance swear, promise, and avow to put our data in the public domain virtually immediately. Insiders will have NO special advantage. We will also disclaim all intellectual property rights to our data. After all, the real intellectual property ultimately lies in identifying molecular counterparts in humans, i.e., the genes and gene products that will hopefully become drug targets, and then finding the drugs that will alter the behavior of these molecules appropriately.

mi: But you are hoping that independent researchers in cell signaling will do more than just read the Alliance Web site and pursue research leads. You're asking for people to register for "membership" to the Alliance. How will members fit into Alliance operations?

AG: The membership represents a third group of Alliance participants. The first group, just to recap, consists of around fifty participating investigators who will monitor and direct progress of the Alliance laboratories. The second big group is the PhD staff and technical personnel who are doing the actual work in the seven Alliance labs (at UT Southwestern; California Institute of Technology; San Francisco Veterans Affairs Medical Center; Stanford University; and the University of California, San Diego);

...we in the Alliance swear, promise, and avow to put our data in the public domain virtually immediately. Insiders will have NO special advantage. We will also disclaim all intellectual property rights to our data.

they will be employees of their host institution, but their time is 100 percent devoted to Alliance research. Salary support for this second group is by far the biggest item in the Alliance budget. It's very important to point out that the "Glue" Grant functions to "glue" together the brains of our participating investigators, not their own laboratories. With the exception of bridging projects, the research of the Alliance is not being done in the laboratories of the participating investigators.

But what we need in addition is a cadre of people—our members—who will take responsibility for one or two or three

molecules—however many they are up to. Members will be our consultants, our experts. If we have questions about handling certain molecules experimentally, we will turn to members for help. And we want members to populate a database about these molecules, providing information about molecular structure and function in a standardized format that we call a Molecule Page. This will be a superb database for the entire community. So far we have 260, maybe 270 members. And we need more.

mi: But the information that you're asking members to deposit into the database—you're really asking them to review information from the literature, not to provide unpublished work from the members' own laboratories...

AG: Yes. This a really important point because this apparently has scared some people off, who thought that we want unpublished information from their laboratories, and that they'd be giving up publication rights by putting data on our Web site. We don't want unpublished information [from our members]. We want literature information. Purely literature information. We don't want them to give up any of their secrets.

Our database will benefit from the expertise of our members, people who absolutely know their molecules. And the Molecule Pages will also be peer reviewed.

Over a hundred abbreviated Molecule Pages (called "Minimolecule Pages") are already available on our Web site. Pat Casey, the Chair of our Membership and Editorial Committee, is currently making more assignments. We expect a list of ultimately two or three thousand molecules. Now, there are lots of molecular databases out there, but their information is generally spotty—it's not acquired in a systematic way. Our database will benefit from the expertise of our members, people who absolutely know their molecules. And the Molecule Pages will also be peer reviewed.

mi: And you think that peer review will add an element of prestige that will attract researchers to register for membership and provide Molecule Pages?

AG: Well, the main reason that members should join and provide Molecule Pages is that the resulting database will be a huge resource for the entire community. If everybody will put in just a little bit of time, the community will have a great resource. You know...an appropriate, academic, scholarly, non-ego-driven, generous type of behavior. And we're not completely naïve here—we're doing our best to give to these Molecule Pages the properties of a scholarly publication. And they should be appropriate for presentation on the member's CV and should have the appropriate impact on promotion committees and granting agencies and the like. We want the Molecule Pages to convey the message that we've chosen the given member to represent pertinent molecules—that we thus have respect for the member's abilities and background. Members will also be welcome to come to our annual meeting, along with our participating investigators and sponsors.

mi: Well, speaking of your sponsors, industry is in fact going to be funding about half of the Alliance budget, right?

AG: Well, it has actually worked out to be that about thirty-five percent of our annual budget of ten million dollars will come from nonfederal sources. We now have six companies that sponsor us: Lilly, Johnson and Johnson, Merck, Novartis, Chiron, and Aventis. Our federal sponsors are the NIGMS, the National Institute for Allergies and Infectious Diseases, and the National Cancer Institute has also recently indicated that they will provide some funding. We also have funding from two foundations: the Agouron Research Institute and a local Dallas philanthropist.

mi: And what is industry's motivation in helping out with the Alliance?

AG: That's a good question, because we cannot provide them with the traditional rewards—rights to intellectual property or an early look at the data. We have tried to convince the pharmaceutical industry that our results will be enormously useful to all of them and that if they all were to participate their financial contribution could be relatively modest. A proper virtual cell will be an incredible

drug discovery engine. In addition, I think that several of the companies that became sponsors had specific areas of interest. One was particularly interested in our modeling effort; one is curious to see if science can be done successfully in this way. Companies who are not sponsors will still have access to our data on our Web site. But we will work hard with our sponsoring companies to help them interpret our data and realize value from them. They should also have preferential access to new Alliance technology.

If everybody will put in just a little bit of time, the community will have a great resource. You know...an appropriate, academic, scholarly, non-ego-driven, generous type of behavior.

mi: You've mentioned the Alliance as a model for non-hypothesis-driven research in the postgenome era. Do you personally find this era to be as exciting as when you started in science? And do you sense eyes upon you to provide a model of how biomedical science is going to change?

AG: Asking me to compare science then with science now is asking for a comparison between a Model T Ford and a brand new Porche. We have all gone much further than we could possibly have imagined. Today's pace is truly heady. Think of what we will learn in the first half of the twenty-first century!

Do I feel eyes on us? You bet. I surely feel the gaze of our sponsors. They are paying the bills with the public's money or the stockholder's money or their own money. They deserve to watch closely and they deserve results. I hope the scientific community is watching closely, because we need their interest and participation.

I'm doing this and enjoying it enormously because it is important, because the time is right to make a determined run at the big picture, and because it's great fun. One of the biggest jobs that I have to do is to be a cheerleader. I should have put money in the budget for pom-poms. A lot of people have a lot invested here: money, effort, careers. I have to do everything that I can to make sure that it works. This is not a casual operation. It can't be.