



## **Dr. Al Kolb, President, The Society for Biomolecular Sciences, 2-8-07**

**Dr. David Lemberg:** Our first guest is Dr. Al Kolb, President of the Society for Biomolecular Sciences, a nonprofit organization dedicated to advancing the science and art of biomolecular screening, internationally. SBS membership includes over 2000 scientists and specialists from over 24 countries. Dr. Al Kolb, President of the Drug Discovery Consulting Firm, KeyTech Solutions, has worked for Beckman, Packard and a number of smaller companies specializing in assay technologies and automation. Throughout his career, Dr. Kolb has been involved with high-throughput screening, with a special interest in assay miniaturization. As a consultant, he assists companies in evaluating, developing and launching new drug discovery technologies.

**Dr. Kolb:** Hello. Thank you for that introduction.

**Lemberg:** Al, thank you very much for being with us on SCIENCE AND SOCIETY today. I'd love to begin by talking about the overall process of drug discovery. Can you walk us through it?

**Kolb:** Yes, I'd be glad to. First, let me distinguish there are really two phases in drug discovery and drug marketing or drug development. And most people are familiar with clinical trials and what happens when a drug comes to market. The part that I'm most interested in is the very early phase of drug discovery, which is really basic research. It starts in universities and biotechs or in pharmaceutical companies, where scientists are doing basic research into understanding disease. From there, it goes into a more intense phase where specific, we call them targets, because a particular disease you're aiming for is a target. And we start to develop that target to do a very effective, cost-effective assay that they can scan millions of compounds to try to find one that might be a drug. It's really a needle in a haystack, as it's best described.

Once something is found that might be a drug — and I'm saying now it might be a drug from the point of 15 years where it's first discovered — it goes into a series of processes where the effectiveness of the drug, whether it has toxic properties are all done on non-animal models. So, it's very early, simple biochemical experiments. Then, it goes into cell-based assays and then, towards the end, just before it goes into clinical trials, they do some animal testing to check if it works as a drug, if it's toxic to animals. If all these things pass and the FDA says, "It's OK. You can go ahead and start the clinical trials," then the really expensive and long trials begin where we're testing on humans. And this is where we have to be quite certain that the drug is going to be safe and effective. That phase, in clinical trials using humans, probably lasts six to ten years,

maybe more. And there are several phases in that. So, how much detail would you like me to get into on all that process or did I confuse you already?

**Lemberg:** Well, I'm still good. It would be great to talk about the details of Phase 1, 2 and 3 trials.

**Kolb:** OK, now my area is more focused in the earlier process but, of course, what happens in clinical trials is very important because clinical trials are difficult. There are a lot of failures in clinical trials. And that's where a lot of the cost of drug discovery comes in. So, what we're trying to do is to find out why things fail in clinical trials and what we can apply from that knowledge to the early phase of drug discovery so there are fewer failures in clinical trials.

A quick look at the clinical trials is the first phase is when they test the drug against healthy people. They are generally young males and they just look at the drug in fairly low doses to see if there are any side effects, any toxicity. And toxicity can include anything from testing liver enzymes to obvious gastrointestinal distress or heart problems. From that point, then they go on to testing in Phase 2, where they look at different doses in people who have a particular disease that they want to treat. And that's where they start to see if it actually works against that particular disease.

If that passes, then they go onto the more extensive Phase 3, where it's tested against large populations and in blind studies. That is where the physicians that are doing the testing don't know if it's a drug or a placebo, that is, sugar water or something that wouldn't have any effect. And if it makes all those hurdles, then you submit to the FDA and they will then approve or disapprove the drug for marketing. And then, of course, there's always follow-up because quite often, side effects are very long-term. So, they may not occur for years after taking the drugs. So, it's a very lengthy and expensive procedure.

**Lemberg:** Al, thank you very much. So, could we look at the overall question of why so many drugs fail in clinical trials? What could be done to make that process more efficient?

**Kolb:** Yeah, that's a critical point, not only to the pharmaceutical companies, but to the public, to the patients. A quick stat, this is just an approximation, but in Phase 1 and 2, about half the drugs that enter Phase 1 and 2 will fail. And approximately 25 percent of them will fail because they have some toxic effect. And 25 percent will fail because they don't work. So, with all the studies that have been done previously on biochemical assays, on assays using just cells and on trials using animals, everything is fine. You get to a human and suddenly, it's toxic or it doesn't work. That is something that is terribly expensive. 50 percent of all drugs fail for these two reasons is phenomenal. So, we really have to work on that.

And the reason, I think, we see that and it's not because pharma people don't know what they're doing, which a lot of financial analysts like to say. You know, "Why do drug companies have so many drugs that fail? What's wrong with them? What are they doing wrong?" It's just we don't have the right models to test. The human system is so phenomenally complex and so different from animals or purified cells that we would grow in a laboratory that we don't have good

models that predict what will happen in a human. If we did, we wouldn't see suddenly, toxicity coming into play or the drug just not working when it worked on the model system.

So, that's the real area that we have to work on. And they are. These scientists are working constantly to try and figure out what would be a good test model that we would be better able to predict how a drug will act in a human?

**Lemberg:** And so, you've identified one of the areas of basic research that might help reduce the number of failures?

**Kolb:** Yeah. A couple of things we're looking at in that industry are things like different diseases, different animals better mimic the human than others for certain types of diseases. So, for one test, a rat may be quite suitable. For another type of disease, totally unsuitable. So, we're trying to narrow that down.

The other is to better understand basic biology. And this is something that's being done in a lot of biotechs and a lot of pharmas. One of the things that the audience may have heard of is systems biology, where instead of looking at individual biological pathways that may, say, lead to an increase in cholesterol, they're looking at how the whole human system works and what different pathways that interact that we just don't know enough about yet. That's the long-term process. But, it's something that I think is going to yield great results.

**Lemberg:** Al, thank you very much. I'd like to shift the conversation and talk about the technological aspect. What are some of the technologies that are used in the drug discovery process?

**Kolb:** You might use an analogy, electronics manufacturing, say, selling and putting together mobile phones, which is a very high volume. They sell millions a year. And these are made in factories so efficiently that if you buy a couple year's service from a phone provider, they give you the phone for free. So, it's because they put so much work into the automation of the process.

A lot of those same things are being done in drug discovery, where a pharmaceutical company may have a million compounds and they call it a compound library, a million different compounds that they would want to test to see if maybe one of them will prevent a plaque build-up in the arteries that would lead to a heart attack. Another in that library may be effective in preventing Alzheimer's disease.

So, when you think of a million compounds to test in a biological assay, that's pretty daunting. And they do that through very similar automation that they would use for making mobile phones or for making cars in factories. Robots completely handle the whole process of doing a biological assay, from mixing the purified components to measuring the read out that would tell you if there's any effectiveness to that compound. And it's done extremely quickly, extremely efficiently and relatively inexpensively.

**Lemberg:** Are there recent advances or is the field of high-throughput screening complete?

**Kolb:** Oh, I wish. If it was, I'd be out of a job. I'm glad it's not complete. Tremendous advances have been made. When I first started in high school, it wasn't called high-throughput screening then. It was just drug discovery. We used to do assays, and the audience may not be familiar with this unit of measure, but they used to do an assay in two or three milliliters. That's a thousandth of a liter. Now, they do those same assays in a millionth of a liter. So, that's a thousand-fold decrease in the volume used, so the number of components are all reduced dramatically. So, that saved a tremendous amount of money and space. And they did that through a very clever technology as to how to measure the assays and in the automation for how they can put all these components together.

But, there are still advances there, but it's fairly well established. Now, they're moving from that arena, which we now call macrofluidics, into nanofluidics. Probably many listeners have read things in the press and on the news about nanotechnology. That's a big developing area where single molecules will be measured. Instead of needing tens of thousands of molecules, things will be done on just a scale that we can't imagine now. It's not in place yet. There's a huge future there.

Some of the other things being done now are in the field of imaging, where you can actually view individual cells or the parts of individual cells, so you can see how change is occurring at the sub-cellular level. And that's going to teach us a lot about basic biology and how cells behave in different situations because when you get down to it, everything our bodies do and the way we react, whether good or bad, comes down to single cells or single cells acting in unison as an organ. So, there's so much being done on that aspect. I have some work that I'm doing on that now and it's just phenomenally exciting what we're going to be able to do with understanding cells and organs at a very basic level.

**Lemberg:** Wow. And so, you might be able to introduce a prospective chemical into a cell and observe changes in real time?

**Kolb:** Yes. That's very well . . . can I use that? That's very well-phrased.

**Lemberg:** Of course! Al, thank you. Well, you mentioned nanofluidics and imaging techniques for single cells. And we looked at nanotechnology. How will this, overall, impact . . . I guess blue-skying a little, the pharmaceutical industry and change or hopefully improve the dynamics of the healthcare system overall?

**Kolb:** There's probably more being done on the diagnostic level, but that's really the critical part of healthcare is how we diagnose diseases and then, how we treat them. Nanotechnologies are being used more in that area than they are in the basic research area. I think that there's more need in the diagnostic area. I'll give you an example of some work I've done in the past. Not personal lab work, but just my interest in the literature.

There's a big program by the National Cancer Institute. Generally, when cancer is detected in humans, it's probably been there about five years. And it's generally detected because there's a

deterioration in health or there's a massive tumor that can be detected. Now, that's really way down the line and quite often by that point, surgical intervention is one of the few ways of treating it, or chemotherapy, radiation, pretty drastic ways to cure a cancer. What the NCI wants to do is to find that cancer in the first couple months. When it's a few cells large, it's very easy to treat. So that I think what they're looking for in nanotechnology is this sensitivity to get that cancer at the stage of the few cells.

**Lemberg:** And it might be assessed on the basis of a biochemical assay?

**Kolb:** Yes, in fact, the phrase they use for that is a biomarker, a biological marker for a particular, any disease. Cancer is one of the big targets of this.

**Lemberg:** And so, let's say a few thousand cells would produce a small amount of a biomarker, which might be able to be evaluated by a nanotechnology-based study.

**Kolb:** That's right. It's all in the sensitivity. But when there's a mass of cells, then it's easy to detect by several methods. But, when it's just those few cells, can you pick up a marker that will tell you that there's a developing tumor there? And then, the intervention should be quite simple. It's easy to say it's simple, but it's certainly, the chances of treating and curing could be very high.

**Lemberg:** Right and so, of course, this is early days for this kind of research.

**Lemberg:** Very early, yeah, but there are techniques being developed that look very promising. So, I think that'll be a big help to healthcare. Along with that, it should be mentioned because it's quite popular in the press now is stem cell research. So, this is a really completely different approach from the current pharmaceutical chemical intervention in the disease. And we're looking at using basic cells to repair problems. And again, it's early on, but the work being done around the world is so encouraging.

And it's amazing the work that they've already been able to do in treating, in some cases, humans, but mostly still animal models. People have shown that you can repair livers, you can repair spinal cord damage using stem cells. And this is going to be such a great method of intervention, maybe not for preventing, but for treating diseases and injuries.

**Lemberg:** Yes, it's tremendously encouraging. In fact, there's a conference this weekend in San Diego and most of the medical researchers there are working on spinal injuries.

**Kolb:** Yeah, I'll be at that meeting. It's in La Jolla starting Monday. There was one two weeks ago in the San Francisco area, so they're becoming . . . well, it is a hot field and it's becoming more so. Put aside all the ethical issues involved in it, I think those can be quite easily handled here in the U.S., as they are in Europe, currently.

**Lemberg:** Yes, we agree. Al, could we talk a bit about personalized medicine? I think that's a natural segue.

**Kolb:** It is. It gets to the heart of clinical trials and why they fail. Why does one person take a particular medicine, say, for high cholesterol and it works fine and he's happy. Another person takes the same medicine. It doesn't work and it damages the liver. Why do those two people react so differently to the same drug? Because we're all different. Why don't animals predict how a drug will react in humans? Because animals aren't humans and two humans aren't the same.

If we could know what drugs worked on what people, we'd have more drugs on the market. When a drug fails now, it's because maybe 10 or 20 percent of the people have a negative reaction. If we could predict what that 10 or 20 percent would be, then they don't take the medicine and the other 80 percent can benefit from it, instead of taking it off the market. So, that's personalized medicine. And one of the ways they're looking at finding that is going back to looking at biomarkers in these individuals to see if we can tell from something we can measure from the blood or from the urine or from some specimen from the human, whether they'll respond positively or negatively.

Another way is genomics. Genomics almost sounds like old hat now because five years ago, it was getting all the buzz in the press. But, it's gone from being something that you hear about in the press to something that's being used on the scientific level to make real breakthroughs in that. So, you look at a person's genome and use that to predict how they'll react to a particular drug. So, it could very well be when you go into the doctor because you have high cholesterol, take a blood test, take some samples, give you a genetic analysis and say, "This is the particular drug you should take because that one will work for you because you have all the genetic profile." Just think how much time and money and agony that would save.

**Lemberg:** That will be great.

**Kolb:** And I don't think it's that far off.

**Lemberg:** Maybe 15 years or so?

**Kolb:** Closer.

**Lemberg:** Really?

**Kolb:** Yeah, I think we're getting in the five-year frame. I tend to be optimistic, but so much changes. Fifteen years from now, we're going to look back. I think we'll be looking back at the 1990 computer, compared to what we have now.

**Lemberg:** In healthcare? Wow.

**Kolb:** Yeah.

**Lemberg:** So, the future for healthcare delivery in medical practice is bright across a range of fronts.

**Kolb:** From stem cells, nanotechnology and diagnosis to personalized medicine, they're all going to have such a huge impact, different timeframes, a huge impact.

**Lemberg:** Al, thank you so much. Well, we've got a little time left. I want to be sure we talk about the Society for Biomolecular Sciences. Can you tell us a bit about your organization and its activities?

**Kolb:** I can. Thanks. I'd like to get a little plug in for that because it's a wonderful organization, a wonderful group of people. It's a non-profit organization, which started in 1994. A group of scientists were at a meeting. They said, "We don't have . . . there's the American Chemical Society, there are dozens of societies for different fields of biology. And for this drug discovery area, we don't really have a place to meet, a place to get together, a group that can interact." So, we started this society with, I think there were ten of us in the basement of a hotel. We got a number of companies to donate some money, as sort of seed money. And from that basement room, we've grown to a non-profit society of about 2000 people. We have a peer review journal, a number of programs, educational programs, grants, scholarships and an annual conference that this year drew close to 3000 people.

And this gives people who are focused in drug discovery, both on the research level, basic biology research to the people looking at all those compounds to find a drug, to the people that are doing early testing for toxicity and for efficacy, it gives them a place to get together and discuss what's working, what isn't working, all the new technologies. We have a very strong technology supplier community that we work with. And it's just a group of people that are so dedicated to what they're doing. Every year, I get refreshed again when I come out of that meeting, exhausted, but refreshed in the sense of knowing that there's a great community of people that are really involved with and dedicating their lives to finding these better medicines. They get very little recognition outside of the community.

Most people when they read about pharmas, they tend to think "Oh, they're selling their drugs for too much, they're ripping us off. People are getting sick from taking their drugs." And those things happen, but it's the people in the research that are just wonderful to interact with. So, when you think of taking that drug, don't just think of some company making money, but think of what they're doing to help you and the tens of thousands of scientists that are just working day and night to bring those things to you.

**Lemberg:** Yes. Al, thank you. And is the next annual conference in the planning stages? Or, are the dates set?

**Kolb:** Oh, we have conferences out years planned. The next one is in April in Montreal. We tend to alternate them from the East Coast of the U.S. to the West Coast and then, to Europe. This year, it's Montreal. After that, it's St. Louis. And then, we're going to go back to Europe again.

**Lemberg:** Al, thank you for a wonderful conversation today. I think really, we covered the waterfront. Our guest is Dr. Al Kolb, President of the Society for Biomolecular Sciences. Thanks for being with us on SCIENCE AND SOCIETY.