

A Biographical Interview with Kinexum Founder and Executive Chairman, Zan Fleming

Kinexers Thomas Seoh and Georgina Xanthou conducted this personal interview of Zan last year for *Kinexions*. Zan has resisted this project at every turn, but the interviewers relentlessly wore him down into agreeing to the following excerpts being published.

Interviewer (I): Zan, what three things do most people not know about you that they might find interesting, surprising, even shocking?

Zan (Z): <laugh> well, I am a shocking kind of person...It might be of interest that I love making things with my hands—furniture making, model ship building, and home renovation. I've built a fair number of reasonably good furniture pieces – a Chippendale style highboy chest, for example.

I: Do you recreate them or do you re refurbish them, or...?

Z: No, I start from scratch with mahogany or cherry boards. I have also restored some furniture, and I've also made a few musical instruments, including a harpsichord and a clavichord. Those were from kits. Haven't done much lately, but ironically, I did most of it when I was in medical school. I had more time then.

I: <laugh> What would you say was the genesis of your interest?

Z: My grandfather had a workshop and I loved to go down and watch him make stuff. He gave me his tools and that got me started.

Z: I also love music, which will not be a surprise to those who have viewed our Metabesity conferences in which we have included shoutouts and performances from world-class musicians. I have been told I'm a pretty good singer but not in my father's class. He was an outstanding soloist. Few people know that I've written the lyrics to a piece that was composed by Allen Pote, who's a world-famous composer. Long story there, but just to say I would like to get back to doing some music and lyrics composing in the future. I also enjoy supporting local concerts and music festivals.

I: You and Sir Anthony Hopkins, who has YouTube videos of his music...and the third?

Z: I am a leader in my local church and denomination—the United Methodist Church. I have served as the lay leader in the three churches to which Deborah and I belonged over the past 35 years. I have given dozens of sermons, commentaries, and lectures in those two large and one small church. I have served in different ways to support the Wesley Theological Seminary in Washington, D.C.

I: Not to give you whiplash, but how did you end up at the FDA?

Z: That is a well-known story because I often tell it. I give credit to our dear Kinexum colleague, Art Santora, who went to the same medical school that I did, at Emory. He was a year ahead, but he was in a MD/PhD program and he ended up a year behind. But he preceded me to NIH where I went after my endocrine fellowship at Vanderbilt. He then went to FDA for a period of time before he went on to Merck. As Art was leaving FDA, he thought of me, about a particular need they had for a clinical reviewer. So, he suggested I apply. I did, thinking it would be a good sabbatical that I would stay for a year maybe, and then go back to NIH or academia.

I jokingly say that I found that I was much better critiquing other people's data than generating data myself in the lab. But it was true...I was not cut out to be a basic investigator. Although I spent four years

doing that at NIH, which was a great experience, I found my niche at FDA. It's because of Art Santora that I ended up there for 12 years.

I felt like I had the best job in the Agency because I lucked into reviews of landmark approvals and was involved in multiple Agency innovations. My first NDA review was the first statin. At the time, I didn't even know what NDA stood for, <laugh> much less how to review clinical data in a sophisticated way. But in my naive way, I pushed to complete the review in what turned out to be record time. I pushed my colleagues and, in some cases, ruffled some feathers, but we set the land speed record for approving an NDA. At that time, the average time was about 40 months. We approved the lovastatin NDA in about 10 months. This led to the center director holding up that NDA review as a model for everybody else at CDER to follow. But I would hate for anybody to see my first NDA review.

That was just an example of sheer dumb luck that led to other lucky things, like the opportunity to be stationed in Geneva at WHO for a year and a half, which was a wonderful, mind-expanding experience. My assigned project was in China, which led to multiple adventures in Shanghai, Shenzhen, and Beijing, that included eating scorpions and other exotic banquet food.

Other opportunities I had at FDA included Leading Reviewer training and education, and this allowed me to get to know people all through not just CDER, but CBER and CDRH. We made that a socializing process as well, like a weekly CDER-wide seminar, and that was a good opportunity to also have some fun and get to know each other. I used to bring refreshments and play music before the start of the program. We could get just about any speaker we wanted. I also co-founded CDER's Virtual Journal of Regulatory Science. It died after I left, but I believe it might have been one of the scientific world's first online journals.

Another thing I did was to demonstrate the first use of the internet for regulatory communication, and that is another interesting story. The first transmission during this pilot project was when I was in Taiwan on an FDA educational mission, and I arranged to receive a small, maybe 15 kilobyte file, by internet dial up - probably took, 15 minutes to get it. But the point is, this was the very first example of an FDA regulatory transmission over the internet related to a review project. It was just my dumb luck to be in the position to be on the cutting edge of that technology at FDA.

I: Before we leave the FDA, we have heard you say that you had to fight for the approval of metformin for treatment of type 2 diabetes?

Z: That's a surprising story because there was so much controversy and even resistance within the Agency at the time. Metformin has since become the first line treatment for T2D. Another closely related biguanide drug, phenformin, had previously been removed from the market because it led to serious cases of lactic acidosis. It was actually the only case in which FDA preemptively removed a drug in contrast to the usual case in which the company removes its product "voluntarily." Then Secretary of Health, Education and Welfare, Joseph Califano cited the imminent hazard provision, and phenformin was removed from the market the next day.

This experience led to very strong opinions in the expert community that the US should never have another biguanide on the market. However, metformin had been used widely throughout the world since the mid 1950's and its effectiveness was well-established. There were an enormous amount of controlled trial and epidemiologic data that showed metformin was not associated with a risk of lactic acidosis except in people with renal failure, in whom the drug could accumulate. The data were compelling to me, but even one of my clinical reviewers violently disagreed. We let him present his opinion at a dramatic advisory committee hearing, but he persuaded no one. We put together an Agency working group to prepare for a storm of criticism. The group included CDER director, Janet Woodcock, who was key for engaging known critics. The storm never came. Metformin remains a major T2D therapy, and now it is

one of the favored interventions for slowing the aging process and reducing risks of multiple chronic diseases.

I: Perhaps ironic is not the right word, but isn't metformin one of the safer or safest drugs out there?

Z: There is that irony. As mentioned, metformin is a favorite candidate for targeting healthy longevity. There is this trial that may get started soon called TAME, or Targeting Aging with Metformin that in part is based on the drug's excellent safety profile. Metformin's safety makes it one of the few drugs that could be tested in a healthier population, for preventing multiple chronic diseases, in contrast to treating a single disease.

I: Let us give you whiplash again and ask how you would describe the family culture in which you were raised? Your dad was a cardiologist? Do you come from a line of doctors? How were you and your siblings raised?

Z: Well, I came from a unique household. My father was a wonderful model for being a practicing physician, but he was much more than that. He was a great innovator and was very much on first name basis with the leading cardiologists of his day and did a lot of things for medicine in the region in which we lived. My mother was a force to be reckoned with, an accomplished writer and a great practitioner of hospitality. She and my dad were quite a formidable couple, and they brought a who's who of famous people to our house for dinner, Christian Barnard, Michael DeBakey, and many other famous physicians, Eudora Welty, Roy De Groot, Frank Reynolds, the ABC news anchor, a whole host of authors, and politicians.

I: This all in the Florida panhandle?

Z: Pensacola, 674 miles from Miami.

I: That wouldn't be surprising if you're talking about Manhattan, but that seems so surprising in Pensacola.

Z: That was another thing my dad did, put on regular conferences, which influenced me to do the same thing. He brought world famous people to speak to local physicians. This was very unusual for a relatively small city in the deep South. Being an old naval town and its over 400-year history made Pensacola unique. My parents wrote together with noted composer, Allen Pote, a musical based on the true and fascinating story of a squadron of large seaplanes based at NAS Pensacola, which made the first transatlantic flight. Unlike Lindbergh, the flight was not non-stop and has largely been forgotten. The play was performed over 50 times, including at the Kennedy Center.

I: If you had not become an MD, what field would you have liked to have gone into? Or was that never a question?

Z: I always wanted to be an architect growing up and it was only when I got into high school that there was a future doctor's club and I thought, what the heck I'll join it. Once I joined it, I figured I'll just go with being a doctor <laugh>, which was probably a good thing because I'm not a good artist. You need to be a good artist to be an architect.

I: Do you have any advice for young scientists and MDs from your vantage point?

Z: Be curious about everything and keep an open mind. There is something to be said about doggedly pursuing a childhood obsession to be a neurosurgeon or astronaut, but chances are that curiosity, an open mind, and persistence will lead to the right place. There are just so many opportunities in science and

medicine that the challenge is choosing among many good choices and not stiving with blinders on to achieve a preconception. Science is a great discipline with which to prepare for a career, even it does not directly involve science. Never stop learning about the world you live in.

I: Another whiplash question: would it be fair to call you an Anglophile?

Z: Well, I love England, but I also love Western civilization, but also Oriental culture. I don't know why England stands out other than that's probably my historical roots, at least, going back four or five centuries, before my Flemish ancestors left Holland. I did spend a year there while my father did a sabbatical at St. George's hospital in London, and that was such a great experience. It was a life changing experience that gave me a love of British culture, music (the Beatles were just catching on), and history.

I: On Zoom calls, including this one, you often have model ships on the wall behind you. <laugh> Are you a sailor, or other sea enthusiast?

Z: Well, I love ships. I used to go down to the harbor in Pensacola just to watch the ships. In fact, I took a job one summer unloading heavy bags of fish meal in the holds of freighters, which was the worst job you can imagine. <laugh>. I just loved the idea of ships in general and sailing ships in particular, but it's also ironic that my family will occasionally rib me about this: even though I love ships, I'm not a very good sailor. I was famous for having run a sailboat, aground <laugh> in Chesapeake Bay, near Annapolis. It required a commercial towing company to take us off the sand bar. It's a story I'll never live down in my family.

I: Was this when you were young, a teenager?

Z: The fish meal loading was when I was a teenager. The long shipwreck story short is that this was a surprise that my daughters gave me for my umpteenth birthday. They rented the sailboat, and we set out with the idea that we would sail to where we were staying outside of Annapolis, and a big storm came up and it led to some confusion. Not on my part, but, uh, the map makers were confused when they <laugh>, uh, they drew the map. Despite my best efforts, the shoreline kept coming at us.

I: So lightning round, are you a dog or a cat person?

Z: <laugh> Both. First a dog person. Deborah and I both had dachshunds before we knew each other. More recently, we had a pair who both lived more than 20 years. We became cat persons along the way. We also claim as our own the pair of eagles who nest over the Potomac behind our house.

I: I believe that you're on the board of a Methodist seminary. How do you think faith and science should relate to each other?

Z: Well, I think they relate to each other because human beings need both, even though they're entirely different enterprises. I do believe we can accept that scientists can be people of faith and people of faith can be scientists and that science and scientists need not be hostile to religion or faith. A good example of that is Francis Collins, who founded the organization, BioLogos, which is primarily aimed at helping Evangelical Christians accept that science is not hostile to their beliefs. That there doesn't have to be a conflict between those who believe in the more literal interpretation of scripture and what modern science is telling us about the universe and about biology and disease. I do see the desperate need to help evangelicals to trust in the methods and findings of science.

I think whether you practice a religious faith or not, human beings have the instinct to believe in something that's greater than themselves. That's where we can all find common ground. We don't have to accept a particular set of beliefs about God or even whether God exists, but we can live our lives enriched

by the appreciation of principles that go beyond what is found in scientific books.

I: From the sacred to the profane: what are your short- and long-term ambitions for Kinexum?

Z: I've always said that Kinexum is a means to an end. That was particularly true when I founded it, thinking that the end would be to identify particularly important opportunities to develop therapies or other life science assets. We did that in the early days: we founded a company aimed at stimulating islet regeneration in people with diabetes and long story short, that effort failed. We then went back to making Kinexum more of an end than just a means - a particular model for offering important needed solutions for small and large organizations that are involved in development of life science assets.

My hope is that Kinexum will be not just a firm, but an important resource that will keep going long after me. To a significant extent, it has developed into an organization that's far beyond what I ever envisioned, and I hope that it will just keep on its trajectory to be a substantial force and resource for catalyzing the development of important products that treat or prevent disease.

I: Just a couple more questions. Do you have a guilty pleasure?

Z: <laugh> I love chocolate. I take some satisfaction in evidence that flavonoids and other constituents of chocolate have health benefits <laugh> but only in large quantities, which cannot be practically consumed in chocolate alone. So I think we have to call chocolate a guilty pleasure *and* not a safe and effective intervention. <laugh>

I: What are you most looking forward to learning before the end of this decade?

Z: I hope to see substantial progress in preventing multiple chronic diseases, particularly diabetes. Preventing type 2 diabetes is eminently achievable now. Preventing is not quite the right word. Let's use the word preempting or reducing the risk of developing the disease. I do think what we can make substantial strides in actually slowing the progression of multiple chronic diseases among people across the globe.