Kinexions

Insights for Translating Life Sciences into Solutions

A Note from the CEO

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Welcome to the Fall 2021 edition of *Kinexions*!

A Note from the Chairman

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Our stellar CEO, Thomas Seoh, has covered the momentous Targeting Metabesity Conference as well as a few pages could

The Kinexum/Kitalys Institute team recently returned from broadcasting over the internet our signature annual *Targeting Metabesity* conference, October 11-14, 2021, from our 'studio' in Harpers Ferry, West Virginia. Metabesity, which has been called "**one of the most important longevity conferences of the year**," with a "**staggering**" speaker roster, occupies a unique 'lane' among longevity conferences...

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possibly allow. Do look at the session recordings when they become available to see for yourself if momentous is a warranted description. I can brag on the conference because I was just one member of a highly committed team that included Thomas, Conference Co-Chair Dr. Larry Steinman of Stanford University, Kitalys Institute Director Adriane Berg, associate Brontë Jenkins, and administrator Kristi Hultberg...

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Artificial Intelligence In Diagnostic Imaging

Craig Sherman, MD, MHA
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In 2015, Klaus Schwab, Founder and Executive Chairman of the World Economic Forum, first coined the phrase, "The Fourth Industrial Revolution," a "technological revolution that will fundamentally alter the

The Amazing Career of Dr. Jay Skyler and His Thoughts About the Future

Interview of: Jay Skyler, MD, MACP
Professor of Medicine, Pediatrics and Psychology at the University of Miami

Alexander "Zan" Fleming, MD, Executive Chairman and Founder of Kinexum Services, interviewed Jay Skyler, MD,

way we live, work, and relate to one another" [1]. Along with other technologies—such as Robotics, the Internet of Things, Genomics, and Virtual and Augmented Reality—Artificial Intelligence (AI) is a pillar of this new industrial revolution that is already shaping the very basics of our day-to-day existence — the way we shop, drive, trade, spend our spare time, date, and more ominously, wage war...

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Professor of Medicine, Pediatrics, and Psychology in the Division of Endocrinology, Diabetes, and Metabolism at the University of Miami. Watch the interview to learn about Dr. Skyler's career, his thoughts on major scientific advancements in the field, and where he thinks the future of diabetes research is heading. For a sneak peak, read some interesting segments from the interview below...

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Early Development Issues Faced by Nearly All Emerging Life Science Companies

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Lest We Forget: Brief Memoirs from a Septuagenarian

Adriane Berg, JD
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It is a challenge for a septuagenarian to write an autobiography in 1400 words or less. There is a lot to tell you. The best I can offer are a few bite-size accounts of important (to

Practically every emerging company engaged in IND enabling preclinical development faces common questions regarding: (i) regulatory strategy and pathway(s); (ii) when and how to make first approach to the FDA; (iii) preliminary target product profiling; (iv) clinical development plans, timetables and budgets; and/or (v) indication prioritization and portfolio planning...

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me) happenings in my life with a flavor of the times in which they occurred. These times are so vivid in memory that I can sense them as I write. Welcome to my own personal Madeleine de Proust...

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Continuation of the Above Articles

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A Note from the CEO (cont.)

...Some conferences focus on the science of extending human lifespan, even by centuries; others on how to make money investing in longevity companies. The mission of Metabesity and its organizer, the 501(c)(3) tax-exempt not-for-profit Kitalys Institute, is to *accelerate the translation of emerging geroscience and other sciences into material, accessible gains in public health, by preventing chronic diseases and extending healthy longevity*. We do this by assembling leaders from a wide range of disciplines for 'silo-busting' dinner-salon-style roundtables, panels and fireside chats on identifying challenges and tractable solutions to accelerate this translation from lab to clinic to market, and from evidence to practice to policy.

The 2021 conference included speakers such as former FDA Commissioner Stephen Hahn (now at Flagship Pioneering), Scripp's Eric Topol, former Human Genome Sciences CEO Bill Haseltine, investor/philanthropist Esther Dyson, National Academy of Medicine President Victor Dzau, former PepsicCo Vice Chairman and CSO Mehmood Khan, prominent geroscientists, researchers in chronic diseases from diabetes to cardiovascular disease to cancer, and their peers in regulation, law and policy, social science, Pharma, Food/Supplements and

Big Data, capital markets and other stakeholders.

Recordings of the sessions were made available to premium pass holders during the week of the conference, and will be released to the public in November. If any readers want to receive notifications about the availability of recordings, they can still register at the website link above for a FREE basic pass and receive post-conference notifications and participate in continuing dialogues on the Kitalys Institute Virtual Campus.

In addition to special "fireside chats" and roundtables, sessions were organized along four categories of challenges: **Evidence**, **Policy**, **Behavior** and **Commercialization**. Superb sessions in **Evidence** included metabolic roots of metabesity, key recent and imminent advances in geroscience, nutrition for optimizing healthy longevity, targeting mitochondria, and biomarkers and biological clocks. In addition, a historic session on establishing clear pathways for healthspan products was moderated by Kinexum Founder and Executive Chairman Zan Fleming, MD. This large and extended session brought together three FDA officials with expert drug developers, clinical trialists and law, policy and business strategists around three case studies: (i) a well-characterized measure of function, gait speed, as a candidate for a surrogate or registrable endpoint, (ii) a novel small molecule being developed to enhance immune system resilience in the elderly, and (iii) a composite endpoint of delay of any of a basket of chronic conditions.

Behavior sessions examined how to foster healthy longevity behaviors (since caloric restriction or exercise mimetics are not enough, without adoption of healthy behaviors) and healthspan equity (since achieving healthy longevity for the wealthy won't move the needle on public health).

The **Policy** track examined global lessons, from countries ahead of the US in the adoption of a national policy on healthy longevity, as a prelude to a session on whether the US should adopt such a national policy, and if so, what should one look like? An interesting recognition was that to achieve a shorter term goal such as extending average healthspan by five years, geroscience is not needed: policies focusing on drivers of health such as tobacco, alcohol, sugar, inactivity and loneliness would do the trick. Thus, panelists articulated parallel tracks that should focus on shorter term, lower hanging fruit, as well as a longer term track for geroscience that targets increases in funding, regulatory reform and legislation to correct market failures (such as lack of incentives to repurpose generic drugs for geroprotective indications and for payers to reimburse interventions today that may only benefit other payers years later).

The **Commercialization** track included a session on new healthcare models focused on preserving health, not just treating illnesses, and an extended session by representatives of larger and smaller companies in Pharma, Food/Nutrition, and Big Data and the capital markets discussing the birth of a longevity industry that blurs the lines between regulated and unregulated products, treatments and prevention, mass and niche markets, and premium-priced interventions and healthy foods-as-medicine covered by Medicaid.

Two fascinating sessions that defied the track categories were one on whether we have reached a tipping point in the global longevity ecosystem (yes, for articulated reasons) and another on how to recruit Gen X, Y and Z to the movement for healthy longevity for all (with panelists from those generations).

As in 2020, Day 4 was an Emerging Company Showcase which featured 20 'metabesic' companies presenting their corporate slide decks, curated by representatives of the capital markets, which invited the audience to invest 1M Metabesity dollars among the presenters, the winners to be announced on the Kitalys Institute website. Also, extending the tradition from the 2020 virtual conference, sessions were punctuated by breaks that included pre-recorded 'shout outs' from politicians (former House Speaker Newt Gingrich and Congressman Jamie Raskin), snippets on Harpers Ferry history, musical interludes, virtual social hours at the end of Days 1 and 2, and the gala celebration at the end of Day 3 emceed by a gifted British comic and extemporaneous free-style rapper.

Targeting Metabesity 2022 is planned to be a hybrid in-person conference (probably in Washington, DC, to be confirmed) simulcast to the internet October 10-13, 2022 – hope to see you there!

- Thomas Seoh

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A Note from the Chairman (cont.)

...You might assume that to bring off this 4-day conference, members of this small team took off from their day jobs for several months in advance of the meeting. Not the case! Kinexum's workload generally accelerates after mid-summer. We have been busy serving important programs across multiple therapeutic areas and product modalities—strategic plans, rescue and due diligence projects, major regulatory submissions, achieving breakthrough designation, and more. We continue to add highly able experts and, in other ways, build capability for serving our clients. We also continue other pro bono efforts—mounting webinars, publishing and peer-reviewing scientific papers, serving on editorial boards, and participating in other conferences.

In short, Kinexum continues to spend as much time working to improve the climate of health product development as it does in guiding clients through the weather around their products. We started in 2001 with orchestrating the workshop and co-authoring the consensus paper on endpoints for type 1 diabetes trials [1]. We continue to foster dialog among experts and regulators in other settings, such as organizing sessions for the prestigious Cardiovascular Clinical Trialist conference in 2019 and 2020, and the May 2021 Symposium on Geroscience

sponsored by the National Institute on Aging, the Uniformed Services University of Health Sciences, and the University of South Carolina.

Kinexum's next push is to help develop treatments for sarcopenia, which literally means having too little muscle mass and the impairments that result. Sarcopenia is now recognized as a disease in the International Classification of Diseases, Tenth Revision, published by the World Health Organization and adopted in a U.S. version. Loss of muscle mass results in frailty, immobility, and much reduced quality of life. It is associated with severe injuries from falls and reduced survival. Muscle mass begins to decline around age 30 and progresses to the point that that by age 70, most people in the U.S. have significant impairment due to sarcopenia. Because of the rising life expectancy across the globe, sarcopenia is one of the least recognized but most important and growing public health and economic challenges of our time.

Sarcopenia, however, has no approved therapies though, similar to type 2 diabetes, diet and physical exercise are important ways of reducing the onset and severity of this condition. FDA has been willing to approve sarcopenia and related indications, and many attempts have been made with a variety of treatments ranging from pharmaceuticals and biotech products to cell therapies. You are surely asking how could this be? The main reason is that safely preserving or restoring muscle mass and function has proved to be very difficult because of the biology involved. Animal models have shown dramatic effects to experimental treatments, but those have not translated in humans. The other reason is that expectations for showing effectiveness are too high.

Soon after I arrived at FDA in 1986, a guidance was developed for osteoporosis drugs, and that guidance was crucial for sparking the development of drugs for that condition. Osteoporosis is highly analogous to sarcopenia in that both involve slow but relentless functional decline of the body's two major structural organs. FDA has not produced a sarcopenia guidance, and some of the advice that it has given sponsors in the past has, in our view, been unreasonable. I am hopeful that FDA will start to modify its expectations and put them into a comprehensive guidance. But, they need our encouragement and scientific input.

Another important reason for advancing interventions to treat sarcopenia is that they could also prove to be preventive. Sarcopenia-preventing drugs could have mechanisms that yield other benefits, such as slowing the onset of multiple chronic conditions. These chronic diseases along with cancer and the aging process itself comprise the constellation of conditions we call Metabesity. Thus, we see sarcopenia treatments as stepping stones to Metabesity preventions. One of the Kitalys Institute's objectives is to establish clear regulatory pathways for interventions that target chronic disease prevention and age-related disabilities. Sarcopenia is among a number of important work areas in which we hope to accelerate the translation from science to public health.

To your health,
- Zan Fleming

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Artificial Intelligence In Diagnostic Imaging (cont.)

...On a more humanitarian note, AI has also irrevocably changed the trajectory of medical diagnosis and treatment, which in turn will have profound implications for healthcare, ranging from local changes in the workforce all the way to navigating global health strategies. AI has had an especially profound effect in diagnostic imaging where at least 125 new interpretive and noninterpretive algorithms have already been approved by the FDA [2]. In this article, we will review the basics of AI, including machine learning (ML) and deep learning (DL), explore specific examples of the utility of AI in diagnostic imaging and medicine in general, and discuss some potential societal implications of this burgeoning technology.

Although the term "Artificial Intelligence" seems like the latest buzzword, it has, in fact, been around since 1955 when Stanford Professor of Computer Science John McCarthy, then at Dartmouth, proposed a summer research conference on "artificial intelligence" based on "the conjecture that every aspect of learning or any other feature of intelligence can in principle be so precisely described that a machine can be made to simulate it" [3]. A more current broad umbrella definition of AI is "the branch of computer science devoted to creating systems to perform tasks that ordinarily require human intelligence" [4]. In the context of medical imaging, AI encompasses the "acquisition, reconstruction, analysis and/or interpretation of medical images by simulating human intelligent behavior in computers" [5]. In other words, the computer algorithm attempts to use both raw and processed imaging data to both improve the acquisition process itself (e.g., reduce radiation dose in CT scanning) and surpass the interpretative ability of the radiologist (e.g., increase detection of breast cancers in mammography and prostate cancers on MRI).

To accomplish these goals, Machine Learning (ML), a subset of AI, is employed to create computer algorithms by inputting "known" imaging data sets that "train" the computer to recognize specific patterns, which can then be applied to "unknown" data sets to achieve the correct diagnosis [6]. For example, if the task is to identify brain tumors on MRI and determine if they are benign or malignant, a series of training images containing known brain tumors is analyzed, first to learn if abnormal brain tissue is present, and then to extract its features on a pixel-by-pixel basis so that the best predictive model of benignity or malignancy can be constructed. Once the algorithm has "learned" how to detect and classify brain tumors, the model can then be applied to unknown cases to help detect and predict whether a tumor is benign or malignant. This "learning" process can be supervised (i.e., the training data sets that are inputted are "labeled" with the correct answer, an arduous manual process) or unsupervised (i.e., the algorithm itself recognizes patterns and correlations on its own, even those which may not be visible to the human eye) [5]. A hybrid approach called semisupervised learning makes use of a large quantity of unlabeled data combined with a usually small number of labeled data

examples [6].

Deep Learning (DL) represents a further subset of ML that utilizes “deep neural networks.” Although DL is not a new concept, recent advances have been accelerated by the increased availability of large, publicly accessible labelled input data sets, inexpensive and powerful parallel computing hardware, and improvements in training techniques and neural network architecture [4]. In DL, input data parameters—such as shape, signal intensity, or edge characteristics of a lesion—are encoded in an informational hierarchy that is distributed through an architecture of artificial neural networks, much like interconnected biological neural systems [4]. Input data is distributed through a series of interconnected “hidden” data layers, where it is weighted and iteratively adjusted to create the best model beyond which no substantial improvement in performance is achieved. Once a computer algorithm is outputted, it undergoes real world validation with unknown test cases. This process typically consists of comparing the performance of the algorithm to a cohort of well-trained “human“ radiologists reviewing the same imaging data.

AI algorithms in medical imaging can be utilized in a multitude of ways, with both noninterpretive and interpretative use cases. Noninterpretative uses include radiation dose optimization, development of large imaging biobanks, creation and mining of structured imaging reports, and body composition analysis for cardiovascular and surgical risk assessment [5,7]. Interpretive uses have a more visible impact on day-to-day radiology practice and workflow. AI can serve as a triage device, alerting the radiologist to cases such as intracranial hemorrhage and stroke that need immediate attention. AI algorithms can also assist with time consuming repetitive tasks, such as tumor lesion measurement on serial CT or MR imaging studies in the assessment of treatment response. Another potential of AI is its ability to provide the radiologist with an immediate “second” opinion and with a more expanded differential diagnosis in challenging cases [5].

Of course, the most promising use of AI in medical imaging is its potential to significantly improve patient care through better detection of common disease states, such as cancer, coronary artery disease, and stroke. Detecting these conditions earlier in their course translates into decreased morbidity and mortality for the patient, and potential cost savings to the healthcare system [8]. One recent United States study from 2017 estimates a conservative cost savings of $26 billion per year for early detection of the most common cancers [9]. Moreover, AI has the potential to reduce the number of unwarranted clinical interventions, one of the criticisms leveled against many screening and diagnostic imaging studies. With mammography, for example, it is estimated that nearly $8 billion is spent annually in the U.S. for follow-on diagnostic breast procedures, including nearly $2.2 billion for biopsies for benign disease [10]. In prostate cancer, screening with prostate-specific antigen (PSA) leads to many unnecessary biopsies [11], and it is hoped that ML applied to prostate MR (incorporating demographic and biochemical data) will enable physicians to make more informed clinical decisions and limit or potentially eliminate the need for prostate biopsy all together [12].

We are at the very beginning of the AI revolution in diagnostic imaging. It holds tremendous

promise, but like any disruptive technology, it will have profound effects on radiology as a profession, medical practice in general, and society at large. Many have already predicted the demise of the radiologist, much like the buggy maker was rendered irrelevant by the automobile. Andrew Ng of Stanford, and Founder & CEO of Landing AI, has stated that a "highly-trained and specialized radiologist may now be in greater danger of being replaced by a machine than his own executive assistant" [13]. However, much like Mark Twain, "the reports of [radiologists'] death are greatly exaggerated." Davenport and Dreyer in the Harvard Business Review state several reasons why radiologists will exist in the decades to come. They cite the fact that 1) radiologists do more than just read and interpret images, 2) AI integration into daily clinical practice is still a long way off, and 3) AI will require trained radiologists to provide the "answer" (i.e., labelled data) as discussed above [14]. Furthermore, according to a recent survey by the American College of Radiology, only 1/3 of radiologists reported using any type of AI in 2020, with only 11% using AI for image interpretation [15]. Limitations preventing the widespread adoption of AI center around inconsistent performance, potential initial decrease in productivity, cost, and lack of reimbursement [16]. That said, successful radiologists will have to accept AI as a tool that will eventually become ubiquitous, learn how to practice alongside it, embrace its productivity benefits, and not be intimidated by this new technology.

Other disciplines in medicine will also be transformed by the increased use of AI in diagnostic imaging. Certainly, for the oncologist, the ability to quantify changes on serial imaging scans more quickly, automatically, and reproducibly will facilitate clinical trials and bring a new level of statistical accuracy to therapeutic response data. Many difficult clinical diagnoses, like detection of Covid-19 pneumonia on conventional chest radiographs, can be facilitated with AI, leading to earlier treatment by pulmonologists and infectious disease experts [17]. AI has already proven extremely valuable to the neurologist and neurointerventionalist in the detection of stroke, enabling earlier time-critical treatment with clot-busting drugs and mechanical thrombectomy [18].

In contrast to these largely salutary effects on diagnosis and treatment, AI poses unique ethical, medicolegal, and societal challenges. According to a 2019 joint statement on the "Ethics of Artificial Intelligence in Radiology," the "widespread use of AI-based intelligent and autonomous systems in radiology can increase the risk of systemic errors with high consequence…Currently, there is little experience using AI for patient care in diverse clinical settings. Extensive research is needed to understand how to best deploy AI in clinical practice" [19]. Use of AI raises many moral and ethical questions regarding data privacy, security, and ownership; age, gender, and race biases in training data sets; proper vetting of the exploding number of AI applications; and questions of liability if an incorrect diagnosis is made or the wrong treatment is instituted based on a faulty AI algorithm. Furthermore, economic disparities in healthcare may be exacerbated by the differential application of AI according to the financial resources of different health facilities and populations.

In 1637, Descartes pondered the attainability of certain knowledge, truth, and existence, and summarized it in his famous dictum, "Cogito, ergo sum" (Latin: "I think, therefore I am"). Nearly 400 years later, we find ourselves still grappling with these same issues, the difference

being that we now have machines and computer algorithms that can “think,” forever altering the way we interact with them and with each other. It is incumbent that we manage this change well with our own “human” intelligence in a thoughtful, measured, ethical, and responsible manner.

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-Craig Sherman

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The Amazing Career of Dr. Jay Skyler and His Thoughts About the Future (cont.)

What was the beginning of your scientific career?

I took a course in college in animal behavior. Although I took it as a psychology course, it was based in the poultry science department. One of the animals that we dealt with were ducks and we hatched them and tried to show that if you hatched a duck and you were there and said, “Hi, I'm your mama” or acted like you were, they'd follow you around. They went anywhere. The experiment worked that we did that in class and I had my two little ducks. And I said, “gee,” you know at the end of the class, I didn't want to sacrifice these ducks. So, I took them home and they continued to follow me about, and they'd go everywhere I'd go I learned. I even took them to the supermarket and they walked down the aisle behind me. But, one of the things I learned was that if you take the duck's nose and you push it to the ground and you take your finger and you move it out straight from it, it focuses on that, and it becomes frozen in that position. It's a way of hypnotizing the ducks by just drawing a little line. I found that to be a fascinating thing and I've always wondered whether that applies to all levels of animals and not just birds, but it certainly works with birds…

How did you become interested in diabetes and how did this passion develop?

The beginning of the third year of a medical school, I took an elective in research in diabetes… This is 1967. So on the wall, there were all these pictures of retina grade A, B, C, D. My job was to take the retinal photographs from the patients—I didn't know whether they were before or after; they just had a number when they were given to me—and compare them to the ones on the wall and give them a grade. Working in a room projecting slides on the wall and looking at

comparative pictures in comparison to them could get really pretty boring after a little bit. So, I asked to go on rounds with Dr. Nicholas Zervis and Dr. Dick Field to see the patients. And lo and behold, here I am a young medical student, what I discover is that the patients were, for the most part, my own age and already going seriously blind from diabetic retinopathy… From that time, at the beginning of my junior year of medical school, I differentiated to a diabetes specialist and focused on that throughout the rest of my career. Even in medical school, if I took in a nephrology elective, I would pay attention to diabetic kidney disease. When I took surgery, I tried to figure out the best way to drip insulin infusions. Everything I did focused on diabetes from then on out…

As an intern, I was approached by Harry Delcher, a young endocrine fellow, who said, we're starting this camp for kids with diabetes in North Carolina because they won't let them go to the South Carolina camp or to Tennessee camp anymore. We're going to do it for North Carolina and South Carolina and since you're interested in diabetes, do you want to come and help me run the place. Well, I started out doing that as an intern and 15 years later, while I was on the faculty and just becoming a full Professor in Miami, I was still going to summer camp every year. I really came to believe that the only way you understand type one diabetes is to live with it 24/7, which is what we did with the kids at camp. As new developments came along, we actually promoted those new developments. We put everybody on U-100 insulin one summer, and we tried to put everybody on to combinations of regular and NPH twice daily when they previously 78-80% of them were on a single injection of NPH or Lente.

And what we had to do then once we made that switch was—we suddenly realized the kids all understood what was going on, but the parents were coming to pick them up. How were we going to tell the parents what to do when their kid had been on one injection a day and now we're on four components of insulin? And we had to instruct their home doctors, who we had discovered from a previous survey, were basically primary care physicians or primary care pediatricians, one or the other in North and South Carolina who had an average of two to three patients in their entire practice with diabetes. We said, did we do the wrong thing by switching it? But, we ended up staying up till three o'clock in the morning mimeographing sheets, where we filled in the amounts of insulin and told people how you change your insulin doses, one at a time, start with the component that controls breakfast, the overnight component, and gradually try to achieve good control by going up and down with the doses. We ended up eventually publishing them and that was my first notoriety that I got because people called them Skyler algorithms to adjust insulin doses.

When you look back, what stands out as something gratifying?

I think the thing that gratifies me most is the team I put together to work with at the diabetes research Institute at the University of Miami. My team colleagues there have duration of time together with me varying between 15 and 38 years. They all stay a long time, partly because they go through six months of probation and if I'm not a hundred percent sure that they're going to be a team member forever, I get rid of them during their probation period because after that, you can't… Fundamentally it's having the right people around as a team that makes things

work.

Over your very impressive career, what stands out as the major advances in diabetes type one and/or type two?

I think the single most important advance that we've had is the development of continuous glucose monitoring.

What about the Diabetes Control and Complications Trial (DCCT)?

DCCT showed the importance of glucose control and that clearly was, you know it's what I believed all along, so it vindicated things. We mentioned Julio Santiago before, Julio Santiago, David Schade, Bob Rizza, and I had written a book in 1983, we started writing in 82, on intensive insulin therapy and how to achieve it. And that really became the method section for the DCCT. The reason I did not become a DCCT center site was because I already believed that glucose control A) was achievable and B) was important; but I was on the policy advisory group for the DCCT. The other authors all went ahead and became centers as well. The DCCT was a remarkable study and now in its 35th or whatever year, is truly an amazing accomplishment in the field that really changed everything. I thought you were talking about new advances from the standpoint of pharmaceuticals and devices when you asked the question… but the DCCT clearly is the most important study that's ever been done in diabetes. No question.

What advances stand out to you as very important?

I think the development of recombinant DNA technology to allow insulin production and then insulin analogs is one of the major scientific accomplishments of the last century. Your former boss at FDA, Sol Sobel, really was the guy who facilitated that because there had been a National Academy of Sciences report suggesting that recombinant DNA technology should not be used because we might be making bacteria that were dangerous. The folks who came to the FDA for Lilly with recombinant DNA technology for insulin, we're going against that National Academy of Sciences thesis. Sol Sobel, who was the chief at the time, recognized the importance of doing that. I don't think that the world today appreciates that every batch of insulin made, had to be biologically tested with rabbits. In the old days, you had to show their hypoglycemic effect… Sobel recognized that we were going to run out of animals as the diabetes need for insulin continues; and we were not going to be able to continue to extract insulin and then have to not only purify but test each batch; and that recombinant DNA technology was a viable answer. But, he said, I don't know anything about it, the science. So, he went out and he hired experts in recombinant DNA technology to join the division or to be consultants to division. And they followed things every step of the way. It was sort of a moving target NDA, where pieces were submitted as things moved along. And it got approved very rapidly after the final submission because the FDA was prepared and was open-minded and interested in seeing advances something, which doesn't always occur the FDA today.

Circling back to CGM…

Well, I was involved with insulin pumps in the 1980s. And this guy, Al Mann came to see me and he wanted to know whether I would be willing to work with him and chair his Advisory Board for his new company, which was called MiniMed. And so I did, and I joined the Advisory Board and then I was on the Board of Directors. And then along the way we developed a continuous glucose monitor, didn't work very well in retrospect; you could only use it for a couple of days, but it was the beginning of a way of changing the way we think about monitoring diabetes... Continuous glucose monitoring now really does work. And I think it's been the most important advance we've had. It's facilitated automated insulin delivery, which still has a little ways to go before it's perfected, but you can get perfect overnight control and avoid hypoglycemia with it, with automated insulin delivery now if you have the right glucose sensor. I think that's the biggest advance in diabetes in type one. In type two, I think GLP1s are the major thing that has occurred because you really can now with once a week control your glucose achieve your targets, lose weight, and help control the type two diabetes. And it has beneficial effects in terms of the cardiovascular risk. that's huge.

If I had to pick three biggest advances: one is recombinant DNA technology to make insulin and insulin analogs; two is continuous glucose monitoring; and three is GLP1 receptor agonists.

What do you see in the near term and the more distant future for diabetes research and clinical care?

I can tell you what I foresee as the kinds of research directions, whether they will work or not is another issue. Let's focus first on type one, and then I'll turn to type two. In type one, there are clinical trials underway, both with human embryonic stem cells that can secrete insulin and with induced pluripotent stem cells that can secrete insulin. They're very early along. I think that we need to see how we can overcome the hurdles of accomplishing those trials before one knows whether or not we'll be successful. I hope we will be. I think it will take having not only the source of cells, but having an environment that the cells don't undergo immune attack, immune attack either from the rejection standpoint or from the recurrent auto-immune standpoint. That means we need to either use immunosuppressive or immunomodulator drugs or appropriately encapsulate the cells or the islets, but still allow there to be reasonable oxygen flow in and nutrient flow in, and insulin flow out. That's not necessarily an easy accomplishment. We have to have a suitable place that we can implant the cells, and that creates some dilemmas of its own because islet transplants are put into the liver, but that's really more of a hostile environment than we'd like it to be. You can put them in the omentum. But, one of the dangers people fear with either induced pluripotent stem cells or human embryonic stem cells, is that they might differentiate to something else after they've been implanted. And that's particularly worrisome with human embryonic stem cells, even though I think they've now been differentiated enough before they put in that the teratoma concern that had existed is probably no longer the case, at least with the cells that are the ones in clinical trials. But because of that concern and the concern of your former agency, they're put in subcutaneously in the flanker, in the abdomen or in the back so that you can run an ultrasound over them and make sure there's no excessive growth occurring. That's a safety indication, but

that's not really a great place to get good beta cell function from the cells in a high enough concentration of beta cells and massive beta cells to reverse diabetes completely. So, the site creates some problems. Vertex is using induced pluripotent stem cells and using them into the liver, just like islets work, with the argument that they're already differentiated and so therefore, they will not differentiate into something else. But again, as I said, that's a hostile environment, not necessarily the best place to test them. Then, ideally, we want to get rid of the immune response too, and you can do that with CRISPR to either create immune evasion where you get rid of the HLA signals on the to be implanted cells and/or immune protection where you stimulate protective immune markers, so that they will survive better after implantation. And those are a lot of things to be asked for.

As the research goes on, you discover more things... There are umpteen challenges that you discover along the way from trying to protect them from immunity to where to put them to how to get enough of the cells. I hope that in my lifetime, I see this mature into a way that we can reverse diabetes with beta cells of one kind and we have an unlimited supply, but I'm not sure how long that will take... I never try to put a timeframe on something, I think that's dangerous, but I hope in my lifetime, I will see beta cell replacement advance... So, those are the three things that I think that I look forward to in type one diabetes: more perfect automated insulin delivery, beta cell replacement, immune intervention; and going along with beta cell replacement is perhaps beta cell regeneration as well, that we may be able to awaken the sleeping beta cells and get them to reproduce. Those are the things I look forward to...

To hear more, listen to the full interview here**.**

Dr. Skyler moderated two panel discussions at the Targeting Metabesity 2021 conference, hosted by The Kitalys Institute held October 11-14th, 2021.

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Early Development Issues Faced by Nearly All Emerging Life Science Companies (cont.)

...Kinexum stands ready to provide as much or as little support as a client needs. At the same time, we pride ourselves on being more than 'a Delphic oracle' that limits itself to answering specific questions posed by the client and instead pose queries to better understand the full context, not just of the client's product development plans, but of its corporate development situation.

We favor an interdisciplinary team approach, with highly experienced experts specializing in the three major sections of an IND application: non-clinical, CMC and clinical, assessing the state of a client's program, along with supportive functional specialists in regulatory affairs and

project management. In addition, we have experts in commercialization, corporate development, government funding, and other disciplines relevant to early stage strategic planning of emerging life science companies.

We typically start with a regulatory pathway assessment. Beginning with the end in mind: NDA drug approval from CDER? (Is a 505(b)(2) NDA possible? Desirable?) BLA biologics approval from CBER? 510(k), de novo or PMA device approval from CDRH? Any combination product issues? What FDA Division would review the program? Are there any special considerations as a result? If there are options, what are considerations for seeking to end up in one FDA Center or Division over another? We do a gap analysis, marshalling the data and documents in hand and what additional items would be needed for a pre-submission meeting or the clinical trial authorization.

For emerging companies, we almost invariably advise seeking a pre-submission meeting with the FDA (such as a pre-IND meeting, in the case of drugs), typically earlier rather than later. A Big Pharma company, well-known to the agency, might skip the pre-IND meeting to directly submit an IND for e.g., a 5th in class molecule where the pre-clinical development pathway is well-precedented. But for an emerging company, it is important to 'socialize' its product candidate, mechanism and development plans and its internal and external drug development team to lay the groundwork for the Sponsor's credibility with the agency. Furthermore, emerging companies are by definition fundraising, and one of the first several questions prospective investors ask is, "have you spoken with the FDA?" The ~20-page written response from FDA in connection with the pre-IND meeting is an invaluable "prop," operational guide and validation of a company's development plan, timetable and budget, quite indispensable, if available, for fundraising.

We are often asked when is a good time to approach the agency about a pre-IND meeting. There is not a one-size-fits-all timeline; rather, the pre-IND meeting is the chance to ask the agency questions about the Sponsor's development plans so that the feedback can minimize the chances of a partial or complete clinical hold upon submission of the IND. The timing for the approach is a judgment call, early enough that the answers can prevent the Sponsor from going down unnecessary 'rabbit holes' that could be avoided, but not so early that the development plans it asks the FDA to comment on are too inchoate.

In earlier decades of the biotech industry, a draft Target Product Profile (TPP) may have been started in mid-stage clinical development and refined with the emergence of new clinical and market data. As management and investors grew in sophistication, draft TPPs started to be prepared earlier to describe the 'aspirational' product label, and broadened to include evolving profiles to position the product for reimbursement, competitive positioning and marketing, partnering, clinical development, regulatory development and other objectives. In our experience, seed and A round companies typically focus on just a couple elements of a TPP, such as the indication and patient populations, efficacy and safety parameters, route of administration and the like. And, they typically do not have a methodical way of thinking about even these critical parameters.

One problem is that an early stage start-up does not have a full management team that can provide drug development and commercialization input for integration into a draft TPP. Perhaps the company is virtual, with a founder and a couple partners. The company could try to cobble together input on various matters from an advisory board. However, important decisions about initial and subsequent target indications, and perhaps prioritization among several programs, and corresponding development plans, timelines and budgets, are needed to guide its expenditures and to know what to ask for from potential investors. Yet, an emerging company often feels the need to prioritize spending on generating data, rather than spending mid-5 to 6 figures in consulting fees to access and develop such information.

Kinexum recognizes this chicken-and-egg problem of needing some pertinent information to get funding, but needing funding to get such information. If you have or know of an emerging company facing this problem, please come talk to us. Based on the experience of our experts and cumulative work on behalf of early stage clients, we can assemble a 'Goldilocks' level of information and analyses (not too extensive to be unaffordable, not too general to be of little practical guidance).

As this article goes to press, we recently completed an engagement that can be characterized in this illustrative case study (with some facts tweaked):

A client has a new molecule X that has entered Phase 1 with the plan to target type 2 diabetes (T2D). Preclinical and clinical data show that X has a similar effect on a parameter relevant to T2D as a marketed drug Y of another class. Interestingly, preclinical data also show a potential synergistic effect between X and the marketed drug Y, particularly in a segment of T2D that is not currently well-served.

As a single therapy in T2D, X would directly compete with Y. While the current market for Y's class of drugs is in the billions of dollars, this market is contracting at a high rate due to competition from ascendant drugs. Our assessment was that X needs additional differentiation to achieve a competitive market penetration, and that the segment that could benefit from the synergistic effect of X and Y; if the preclinical data are confirmed by clinical data, it could constitute a significant market segment. Reported business development activity supports the potential for growth of this segment. Furthermore, we proposed a course of clinical development that could rapidly and efficiently provide confirmatory clinical evidence for the preclinical observation.

At the same time, we were intrigued with preclinical data with X in NASH, for specific reasons based on our knowledge of mechanisms in pre-clinical and clinical development. We prepared illustrative development plans, timelines and budgets for X in combination with Y for an underserved segment in T2D, and for X in NASH, and some opportunities for savings to pursue both indications in a common development path up to a point.

We supported this assessment with forecasting based on solid understanding of current major

geographic markets and our scan of product candidates in clinical development. Based on internal models that we have developed and maintain, we were able to quickly generate a pro forma model for the client that could support internal portfolio management and possible partnering discussions.

Glossary:
IND: Investigational New Drug
CMC: Chemistry, Manufacturing and Controls
NDA: New Drug Application
BLA: Biologics License Application
PMA: Premarket Approval
CDER: Center for Drug Evaluation and Research
CBER: Center for Biologics Evaluation and Research
CDRH: Center for Devices and Radiological Health

-Sam Collaudin and Thomas Seoh

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Lest We Forget: Brief Memoirs from a Septuagenarian (cont.)

Summer of Love: I graduated from Brooklyn College in 1969 when the Haight-Ashbury Council was formed, and the official Summer of Love was declared. There were 5000 students in my graduating class. My English class alone had 250 students and a teacher with a megaphone so we could hear him.

The graduation ceremony was held outdoors in the pouring rain. Dye from our robes and caps colored our faces. My hair was as purple as a punk rocker's mullet. We moved our tassels and thousands of hats sailed in the air. We felt the full force of the size of our generation, the Pig in the Python, 78 million of us Boomers. It was exhilarating. We expected to live forever and learn how to fly.

But, things were not all roses in the '60s for female students. Most Ivy League and premier colleges did not accept women at all. Harvard sent me a friendly letter saying I was 10th on their women's quota list. Vassar gave me a full scholarship, but I was only fifteen when I started college, and Mom wanted me closer to home. So, I did what all my friends did; I went to Brooklyn.

There was the Summer of Love, the Beatles, NOW, and antiwar protests. I was arrested twice. Later, in law school, I wore an armband that read "Legal Observer." I went with the marchers to Washington and chronicled police abuse. I was tear gassed, which was a badge of honor in those

days.

The Origin Story: My parents met in the mid-1930s and were an unusual pair. He came from an educated family with a real estate agent Dad. She was from a family devastated by the Great Depression. My grandfather and his two sons became plasterers and bricklayers, moving around the country wherever there was work. Mom was twenty-five when she met my father, who was only nineteen.

What they had in common was ferocious drive, intelligence, and a desire, like the characters on the old TV show *The Jeffersons*, to move on up. My father decided to become a CPA, go to law school, and eventually run for political office. My Mom would be his helpmate and right-hand "man."

There was a hitch. My father stuttered so severely that he was taught to stop in the middle of a word until he could articulate the next sound. Some of the interludes were interminable. However, despite it all, they made their dream come true.

By the time I was eight, Dad was practicing law at 16 Court Street in Brooklyn with his partner Abraham Beame, who would eventually become the Mayor of New York City. Dad ran for office, too. What a sight. He would stand on a podium with his speech in front of him, and a hired man would read the words as Dad gestured to the audience. He won the District Council office and was a Delegate to the Presidential Convention of 1956. I still have a little Donkey pin with green stones in the shape of '56 given to all Delegates.

By the time I was eleven, Dad was dead. He died very suddenly. I went to school. He shaved. He said to my mother, "I think I'm having a stroke," and fell on the floor with a fatal cerebral hemorrhage. Next month will be the sixth year of my volunteering at Good Grief, a place helping children who lose a parent at an early age. He was forty-two.

How I Won an Emmy (local): When anyone reads my resume, the first thing they ask me is, "How did you get on OPRAH four times?" Well, it was an accident. After eight years at Wall Street law firms, my husband Stuart and I opened our law firm on Park Avenue South. I specialized in trusts and estates, especially for divorced women and gay couples, to protect their rights.

My Law Review article championed extending the Family Court Jurisdiction to unmarried couples, and the Appellate Division cited my work in doing so. That opened the door to gay couples being considered a family and then a domestic partnership.

However, they still could not marry. I engineered adult adoptions so same sex couples could become legal heirs. I also had many wealthy women clients being bamboozled out of control of their money by trustees, ex-husbands, and adult children. It was time people, with any amount of inheritance, large or small, learned to protect their assets.

I created a course for The New School for Social Research called, *How to Be a Successful Beneficiary*. I never dreamed it would be the seed for a financial show on radio and TV. Here's what happened.

One of my New School students was a publisher and asked me to write a book on the topic. The result was *Moneythink*, the first of a dozen books I have written. To promote my books, the publishers sent me on many book tours. I appeared on Regis, Good Morning America, The Home Show, Morey Povich, Donahue, Sally Jessy Raphael, and many others.

Eventually, I was discovered by a talent scout for WMCA radio... Yes, I was one of the "Good Guys" and one of the first radio financial talk show hosts. When WMCA was sold, I became a weekend host on WABC with friends like Rush, Hannity, and Joy Behar. I was a member of the famous Friar's Club and joined AFTRA. My new occupation was "media personality."

My children's money books were translated into five languages. My 2008 book, *How Not to Go Broke at 102*, Wiley, led to an invitation from Pulitzer Winner Dr. Robert Butler to become an Age Boom Fellow. I was part of the growing age-beat press.

From that, I was invited to be a guest on OPRAH. When FNN, Financial News Network, now CNN, was established, I was the natural host of IRS Tax Beat, jointly sponsored by Excedrin and the IRS... YOU CAN'T MAKE THIS STUFF UP!

And that's how, after four years on TV and four times on OPRAH, I won an Emmy. Today, I host the weekly podcast *Generation Bold, The Fountain of Truth*, interviewing celebrities, scientists, and policymakers. I can produce the show from anywhere in the world, which is a good thing because I am a nomad at heart.

I Nomad: I have visited over ninety countries, many of them several times. This obsession with travel started when I was twelve. Mom sent me to camp in Israel as an antidote to the trauma I suffered at my father's sudden death. In those days, El Al could not go directly from New York to Tel Aviv. The plane needed to refuel in Amsterdam on the way in, and Paris on the way home. We kids spent a few days touring each city. Yemen and Israel were friendly that summer, so the experience would include a student exchange as well. Therefore, I was in four counties in six weeks, at a time when most kids had never been on an airplane.

Travel still makes me feel that rush of awe that eliminates sadness and depression no matter how tough the going. I am writing this article on a KLM flight from Edinburgh to Amsterdam, then to Atlanta and LA. On my way to the plane, I played my favorite game. I looked at the flight schedule to see if I had traveled to all the listed destinations. I almost made a 100% score. Of the twenty flights, I only missed Abu Dhabi, but I'll fix that.

Age Equity: I view my work as Executive Director of the Kitalys Institute as the real-world vehicle through which everyone, and I mean everyone, can have more years to live and continued good health during those years. Yet, I must confess that I am the last person you

would pick as a cheerleader for aging well.

By my forties, I was a cardiac cripple, popping beta-blockers to forestall tachycardia. Four times, I had my heart stopped with Verapamil and then had its rhythm reset and revived. The feeling as you go under for that second of heartlessness is a scary descent into oblivion. I never thought much about making the most of older age; I was sure I would not live long enough to care.

Then, something happened. I gave birth at age forty-four to my second child. I was overweight and tired. I remember that I could not walk more than three minutes on the treadmill. By the time Rose was a toddler, I could no longer tolerate my inability to be an active Mom. I changed it all without a magic bullet: exercise mixed with the right food, sleep, and self-care. I have been a speaker for Tony Robbins, and I buy into the line, "The bigger the why, the easier the how." Rose was my big why.

Today, I weigh 113.2 pounds (yep, I weigh myself every day). I hang on to every word of the geroscientists I meet through Kitalys. They agree that lifestyle is a longevity gamechanger. I am now a long-distance walker… I can walk 50 miles in a day non-stop… no lie.

All this self-care cost money and the incredible longevity breakthroughs to come may be even more expensive. Healthspan must never become the privilege of the wealthy alone. Thus, I am a fighter for Healthspan equity. I am on the Communications Committee of the United Nations NGO on Aging, seeking to develop an International Convention on Age Equity. Additionally, the Kitalys Institute's Targeting Metabesity Conferences and webcasts bring Healthspan equity leaders together to brainstorm solutions. I am proud of every one of our participants.

Gusto Living: The world has changed since the Summer of Love, but one thing remains stable – the potential for each of us to change the world. I end my weekly podcasts with the inspiration Mom gave me, "Get out there kids and make it happen." So, what are you waiting for? As Mom would say, “My money’s on you.”

-Adriane Berg

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