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Keynote Address
My 5 Top Reason for Not Cloning Graduate Students

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I want to tell you a little about where I came from and what I have been doing. I guess I should start with my life story, so if you have heard it before - that's one thing that won't change. So much of my life has been at the Science & Technology Center at UGA. The Center was started with a \$25 million grant from the National Science Foundation and we work together with the Massachusetts Institute of Technology, The University of Illinois and Georgia Tech. The project established research opportunities for early K-12, undergraduates and graduate students educations. They all do research all at the same time. This helps fill the pipeline for future scientists. We need to fill the Pipeline.

So, this is my story or part of it.....I cloned rabbits in graduate school and at the same time my wife and I had twins (Phillip and Claire). Exciting times for me. I was accused of taking my work home with me. This was an anxious time for me, but it helped me focus as a graduate student and also made me very anxious about the future. I tried not to get complacent or comfortable, so this is what I did with my group (of graduate students)- they need to move their science forward at a fast a pace as possible; they need to move their career forward. I completed my PhD in 2.5 years because I needed to get out of there and make some money. I don't recommend having 3 children while in graduate school; but it was a great motivator for me. Let me back up so I don't forget anyone - my wife is Tracey; my children are Phillip, Claire and Danielle. All of them are doing great.

So I have a great basis I think for experiences and I have tried to move that on to further areas in my life. After my graduate degree I went on to animal cloning and then later stem cell work at our large Science Technology Center.

Here is a slide of George, Charlie, Albert and Theo; Sam and Josef came on later. These are cloned calves we produced, when I was Chief Scientific Officer at Advanced Cell Technology. We had a strong relationship with the University of Massachusetts at that time as well. James Robl was involved with that research along with one strong graduate student, Jose Cibelli, who I was co-training and advising. He was very instrumental in getting this work done there.

In my prior position we were doing some cloning work - really didn't work very well, we weren't getting the pregnancies to go on - so we needed to switch and change cell type and step by step, making sure everything is working. That makes for a good scientist. At the same time Jose was saying "we really need to see if these cloned embryos are viable as no one has ever cloned an adult animal before - this is really chancy". I was not comfortable with Jose saying such, but eventually he did convince us to transfer the embryos into a recipient animal and see

how far the pregnancy would go. Lo and behold, they made it all the way thru the pregnancy. Three months into the pregnancy we got wind of Dolly the sheep. Dolly was the first clone - depending on whether you time that as the time the embryo was transplanted. Gestation in cattle is 9 months and sheep is 5 months. So we were right there with Dolly. But that's ok, it was a great event and very rewarding also.

Jose Cibelli, the graduate student, was fairly instrumental in getting our research to excel and take chances and going beyond what we were thinking we were doing. When the news was released, this was the top story on the CBS Evening News. My kids were about 4, 5 or 6. I do remember very vividly them going up to the room where we did the press release - they said " that's great Dad, can we now change it to another station?" At the same time, family can keep you humble as well. The timing was very interesting as this was the same time that President Clinton was in office and if you remember back in time to 1998, some of the events of his folly and our research were breaking at the same time. We initially had an invite to go on the Face the Nation and Meet the Press. The excitement lasted around 3 days, that's when the Monica Lewinsky story broke. People were more interested in Monica than George and Charlie, which is fine - it worked out great.

We have been here for 16 years. Some of our, early work on cloning at UGA used tissue from dead animals. George and Charlie are from live animals. I found it much easier to convince people that all Black Angus that are cloned are not all black. As you see in the slide, all the ones at the top have different markings due to epigenetics. I can't remember all of these guy's names . I do remember "Dumpling" at the end. But a lot of graduate training involves this kind of work over the years. I will briefly mention some of the success stories I

As mentioned earlier, Jose Cibelli, now a distinguished professor and Michigan State, took over a position at Advanced Cell Technology after I left. They are now the only company using pluripotent stem cells for regenerative medicine. Jose was very instrumental in that type of work. Jose's publication at the graduate level is quite unique. Our research on the first cloned calves was published in *Science* and then Jose's work on Parkinson's Disease was published in *Nature Medicine*. His work in developing stem cells from embryos was published in *Nature Biotechnology*; So, two (2) Nature and one (1) Science articles for Jose's graduate work was pretty good.

More recent graduate from my UGA lab is Jenny Mumaw. She is a unique situation as she did her undergrad at UGA, her PhD in my lab and is getting a DVM as 4th year Vet student at UGA. I guess she will be a Triple Dog at the end. She's done great publications. Some of the work Jenny came up with early on is to develop stem cells in combination with hydrogels. This is engineering and genetic engineering. This work allowed us to fix a broken bone in a rat at the 2 week period has been very instrumental in moving this forward with larger animals at the Vet School. This is all based on Jenny's work. We have a new company at UGA that is commercializing this technology for fracture repair in dogs and now humans too. Working very closely with the veterinary side so, she had the most collaborative publication as anyone in my academic lab.

I do want to mention Frank West. We did the old bait & switch with Frank when he came to UGA. He came here wanting to do cloning on endangered species, but there was not a whole lot of research money available for that these days. So, I was recommended he work on stem cell fields, developing stem cells in the reproductive side, sperm and egg cells. He is now an

Assistant Professor in the department - He has now turned the table on me and is working on endangered species, developing stem cells for spotted leopards and endangered birds, and fowl. It is quite the menagerie of animals and humans.

So that's my story that I wanted to share with you info on the Science & Technology Center and where we need to go with our graduate programs. Probably, many of you are knowledgeable about the National Science Foundation and the Science & Technology Center; \$25 million over a 5 year period, at least half of those resources are on the educational side. Graduate students, K-12 and undergraduate conduct research to combine stem cells - and an engineering approach to make biological machines. So the idea is that we can start with a stem cell and then grow it into a machine that can talk and that can walk, but we could possibly do a lot of different things with it. There are various applications for this technology. This has been a good learning experience of teaching graduate students good practices in research areas. This is some pictures to show these ideas.

Here is a slide of muscle cells controlled by neurons and so you can have memory in these machines. These muscles remember through the neural network where they have been, come back to that area or avoid it based on a learning experience. Then working and understanding how stem cells differentiate. So it is really a merging educational and research side - emergence of stem cells into biological machines.

So the graduate education side of the Science & Technology Center is extensive. There are courses that are shared between universities: UGA, Univ of IL, MIT and a Video Virtual Journal Club that we conduct every month. The graduate students all collaborate virtually, practice their presentations and present their materials to each other. There is a lot of communication between the students and I think for a graduate researcher this is the key - the interaction between student and what they can learn from each other and having critical mass that can feed off of each other.

The goals of the Center are career oriented, so not only do students conduct research, they are also very involved in different aspects of research - they have the opportunity to visit labs around the world. They have to conduct research and reach-out to K-12 students. We actually have mock-ups of the biological machines. We go to science fairs to show and this is all done at the graduate student level. They are expected to transfer that knowledge between the students and the institutions so this is a multi-institutional project. I think it is also very important to understand that we have courses on Intellectual Property Ethics and Patent Law as well as Entrepreneurial Activities. We sponsor retreats are the mostly attended by and are most influential for the graduate students because many of them are going on into industry - and this is very important engagement in research.

This is a slide Brian Williams, a grad student at the University of Illinois; we have an exchange of students in my lab. If these movies were working as they should you would see swimming Bots or biological machines. It is very important to understand engineering principals that go into this and models - so they can actually predict the movement, speed and direction of these biological machines through the modeling process they have developed. This is more of an inchworm thing that moves across the bottom of the dish, light activated or epigenetics. And there are high-end publications on these high-end collaborative types of projects.

So the person I wanted to talk about in the graduate program is Ray Sweetenburg. He is a graduate student in my lab and he is an example of where we need to go with graduate research. Where he has really benefitted is in collaboration with Doug White, a computer modeler at

Georgia Tech. The graduate students together came up with a process to predict the differentiation of a stem cell to a motor neuron. This is just a simulation of that (slide) the green cells that come up eventually are the motor neurons - cells that control all of our movement. This was very important to understand the differentiation of those and the use in research for Amyotrophic Lateral Sclerosis (ALS) or Lou Gehrig's disease.

Based on all of this research there are new questions that come up that go against much of the dogma on the differentiation of cells. Ray is working on imaging and experimental procedures with stem cells in a dish/understanding which cells differentiate/ measure the outcomes and starting to model with Doug White. Together, they are getting mechanistic insight into solving the process. Ray could have done a great project on just understanding the molecular mechanisms for differentiation. But, through combinations in EBICS (Emergent Behaviors of Integrated Cellular Systems), we are coming up with new ideas. This is exciting and encouraging.

Ray is taking risks. Ray is starting to learn more about modeling and outcome based modeling systems, but has a lot more to learn. But we are getting ready for an EBICS retreat, we get together every year with our grad students. Ray is involved in a contest with MIT/Univ of Illinois. He developed design principals for Biobots and Ray came up with the idea of using cell death to understand how things change in form, function and design principal. Ray was talking to me the night before the contest and I told Ray he didn't have a chance in winning, " as you are coming up against the engineers from MIT and the University of Illinois and I'm sure they really have some great ideas." Ray said "I think I got a chance and I think we can do this." So, the next day at the presentation when he won, he made sure to call me out as I wasn't sure it was gonna work. So - that was great and very rewarding. Again, it is important to be anxious and to take risks.

The continuum of education, K-12 to Post-Doc research, EBICS also melds with the diversity in recruitment. At Georgia Tech we are working with their programs in grades 8-12. Students actually come in and do research much like our Young Scholars program every summer. But the students are in Atlanta from some of the most under-represented schools, come in during the year and do research. We have a number of programs like that feed the Pipeline all the way to undergraduate programs. These students are being recruited directly to a number of these institutions with our help. UGA needs to make the connection to that Pipeline and the research experience across institutions. We have UGA students doing research at MIT and Georgia Tech. They are recruited for graduate programs, so really say this is a great Opportunity to fill the Pipeline. One goal of the Science Tech Center is to increase under-represented minorities in our programs. We have a very strong process to recruit these students along this Pipeline as well.

So it is intervention, repetitive contact and mentoring of these students over time

My five reasons for not cloning graduate students - there are many reasons- you can imagine. Many times they (graduate students) prove me wrong so I don't want them to be clones. I think one of the things today, as we have the group breakout sessions - I am reading this book now "Wiser: Getting Beyond Group thinking to Make Groups Smarter" by Reid Hastie and Cass Sunstein. Sunstein was an advisor in the White House for the Obama administration for around 5 years and did oversight for a number of different agencies from EPA to USDA and is now at Harvard. It's an easy read, I really recommend it, but it builds on Irving Janis. Both public and private groups wander not in spite of group deliberation, but because of it. I am not trying to put

a downer on today. It goes beyond criticizing and shows ways to improve group thinking/diverse thinking.

5. We want graduate students that are ANXIOUS and we need folks that are not complacent so we have students that can find new ways of looking at things and what they need to know.
4. They encourage diversity in many different ways - background, animal science, biochemist..... At one time I think I had more vegetarians in my lab in the animal science department than non-vegetarians. Lots of diversity and I think I gave you a taste of what we have been able to do in that area.
3. Avoid Hindsight bias.. Cultivate Free thinking. Risk Taking. No bias on what happened before in the book they call this informational signals. Many times I have students that will not speak up or won't tell us what we want to know - because they don't want to disclose something that might be contrary to others; That is something I try to get past really quickly, we don't want clones of those people.
2. We want people that will voice their opinions and actually have a contrary opinion at times.
1. We want to avoid those social pressures - we don't want students that just go along with the herd because they feel foolish or disagreeable. Ray is a good example of that - he was against what I thought was a better project and yet he was unafraid to do that.

I like to sit back and talk and think with my grad students and ask them to tell me something I don't know, and that is very important. I like this statement, I wasn't the one who came up with it but often times " A week in the Library can save 6 months in the Lab"; That is very true most of the time, to know what has been done before you. But sometimes this is false; A lot of students really excel when they can find things that they can go against the dogma.