

# Over 40 years of mentoring, educating, and researching in the world of oocytes

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**ABSTRACT** David Albertini has dedicated his life to illuminating our understanding of the most wondrous of cells - the oocyte. Beyond his powerful scientific contributions, he has mindfully and tirelessly mentored and educated scientists and clinicians in our field. In this essay which reports a dialogue, David Albertini shares some of the key experiences that have governed his career path. He has been a spokesperson to the public to ensure the accurate conveying of current findings in our field, and he has always strived to help others in communicating effectively. He also reflects (notably in light of where funding priorities may lie) on the imperative to use animal model systems that will be most suitable for addressing the pressing questions of reproductive biology today. Dr. Albertini pioneered the use of live cell imaging approaches over 30 years ago, and he has eagerly passed on his expertise to many others while these techniques were in their infancies. His career has been fueled by his passion for visualizing cellular events in live cells and tissues, as never undertaken or seen before. He took chances while always embracing opportunities as they arose. Dr. Albertini has also delineated the intersection between basic research on the oocyte and emerging trends in reproductive medicine - such as oocyte cryopreservation. Not only does he continue to advance the field of human oocyte biology, but he is also, and yet again, extending his role as educator and mentor by taking a lead in reproductive medicine as a journal editor and as a mentor to young and rising clinicians in the field.

**KEY WORDS:** *dialogue, Albertini, oocyte, education*

## Introduction

It has now been 10 years since finishing up my PhD in David's laboratory at the Tufts School of Medicine, and one reason why it never seems that long ago is because of David's voice continuing to resonate in my everyday career. I have learnt from David for the past 15 years, yet lessons aren't over either. David has a wealth of knowledge and experiences for us to learn from, and I am only one of the many students and mentees feeling his impact and appreciating his rooted passion for the field.

I had the privilege to complete this interview while at the 45<sup>th</sup> Annual Meeting and 18<sup>th</sup> Ovarian Workshop of the Society for the Study of Reproduction (SSR) on the beautiful campus of Penn State University in State College, Pennsylvania. SSR is the first conference that David took me to as a young graduate student, and I have been a member and regular participant ever since. SSR exemplifies the excellent and fun science that can come out of productive professional relationships. We've all started as

trainees, and you can always enjoy seeing at SSR even the most prominent and veteran experts interacting with trainees, no matter their levels of training. I could not thus imagine a better place to conduct this interview with David, himself a life-long mentor and supporter of his trainees. David continues to support and mentor beyond the formal training years, and he genuinely enjoys doing so, in turn inspiring the same passion and the imperative to have fun while doing the science. I never forget David's response when I approached him about taking some time off for vacation; this was my first year in his lab, I didn't yet know David well, and I was a hesitant and nervous graduate student. His response was fantastic and attests to his work ethics and motto throughout his career; he replied instantly: "As long as you love what you do, of course you can take the time off!". And so I did, I took time off and importantly continued loving what I do. Of course, I never took for granted this utmost level of trust and professional support from a mentor.

*Abbreviations used in this paper:* JARG, Journal of Assisted Reproduction and Genetics.

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**Before jumping into our conversation, could you give us a roadmap of your career and some of its highlights?**

While an undergraduate at Marquette University, I became exposed to the rudiments of cell and developmental biology through my professor, Tony Mahowald who was kind enough to guide me into the laboratory where I got to conduct research on the composition of poleplasm in *Drosophila* oocytes. His mentorship dovetailed nicely with my summer jobs with Dr. Arthur Hertig, himself an "oologist" of note (though I never appreciated at that time how seminal his contributions with Dr. John Rock were in the 1940s and their classical descriptions of early human development). Coincidence perhaps, but the confluence of these experiences heightened my interest in oocyte biology and it was Dr. Hertig who aimed me to the laboratory of Dr. Everett Anderson for my graduate studies. Andy's laboratory was a hotbed for research into the structure and function of oocytes from many kinds of organisms, and the rigors of experimentation and expectations of excellence in conducting electron microscopy were without a doubt formative challenges that he set before me were I to pursue a career in biomedical research. His insistence that I take the MBL Embryology course in the summer of 1971 cemented what has become a lifelong interest into the biology of this most unique of cells—the oocyte. Our laboratory moved to Harvard Medical School early in the winter of 1972 where Andy set up his laboratory in the newly opened Laboratory of Human Reproduction and Reproductive Biology. Here among many prominent scientists like John Biggers, Don Fawcett, Paul

Wassarman, Ken Ryan, and Claude Vilee my graduate training would be completed in an environment unrivaled at the time for spawning a generation of reproductive scientists fortunate to have walked those hallowed halls of the LHRRB.

Wanting a more biochemical background, I set off to postdoc with Dr. Richard Berlin at the U. Conn Health Center where I was to become a tubulin biochemist and be introduced to the wonderful world of fluorescence spectroscopy, applying at the time the new technique of fluorescence resonance energy transfer (FRET) to understand protein-protein interactions during the process of microtubule assembly.

In the mid to late 1970s, academic positions were relatively easy to find and I returned to Harvard Medical School as an assistant professor in the newly forming Department of Anatomy and Cell Biology being built under the leadership of the late Betty Hay. My peers and I benefitted greatly from Betty's strong desire to make her department the very best there was in the fields of Cell and Developmental Biology and it should come as no surprise that Betty's academic children from those days now occupy positions of prominence around the world.

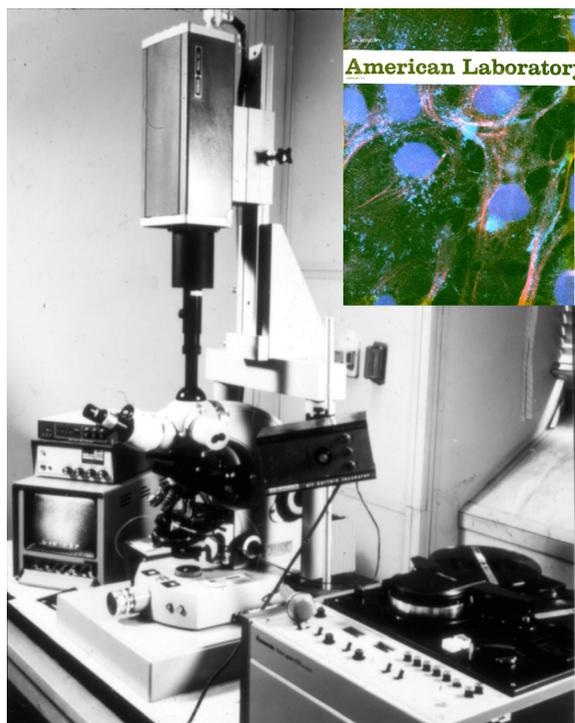
My fortunes continued in having the chance to move to Tufts University School of Medicine in 1984 where I spent the next 20 years doing teaching, research and administration and mostly enjoying training the many students and postdocs in the context of a spirited and collegial environment that persisted until 2004.

My latest position at the Kansas University Medical Center provided the opportunity to build a gamete research program within the context of the Center for Reproductive Sciences.

**Ever since I have known you, you've always been a voice in our field, one that would never be afraid to speak up to the media, and took to heart a need to represent a fair view of science; you've done so repeatedly over the years and about a multitude of topics. Could you share past experiences and perspectives for all of us to learn from?**

The public perception of science is one of those things that we leave up to a subset of scientists to communicate with journalists. This is always something that I have encouraged students to begin to feel comfortable doing and it is also getting to be a more significant role that young scientists need to play. But the problem is that we are not taught how to interact with the public. I often use the example of if you can explain what you are doing to your grandmother, then you've taken a step forward. If you can get your grandmother excited about what you're doing and actually get down to a level that she can begin to understand, then it means that you've gained perspective and vision of the importance of your work.

The second thing is that before you can speak to anyone in the press or before you submit any opinion piece, you really need to know what you are going to say and how you are going to say it. Because if you are not clear, then the journalist will ask more and more questions and you will find yourself walking down a road that has nothing to do with the original topic thus encouraging the journalist to interpret things their way rather than the way that you'd like them to be. One good example was when I was at Tufts with Eric Overstrom and Karl Ebert. We were measuring the DNA content in polar bodies and embryos after vital staining with Hoechst dyes, and way back then we saw this as a possible chance to monitor when during the course of development errors



**Fig. 1.** Time lapse imaging system developed in the late 1970s showing a Zeiss upright microscope with a Venus Scientifics image intensification camera mounted above and supported by a specially designed stand that would bear the weight of the camera. Note from back to front a video monitor, the microscope with air curtain for maintaining stage temperature, and the 0.5 inch reel-to-reel time lapse video recorder. Insert shows cover image of a triple labeled granulosa cell culture published in 1982 with Brian Herman and Phil Presley.

in chromosome segregation were taking place; we were just going to ratio total DNA signals. The first thing that happened was that Discover magazine found out about this and they sent a journalist and what resulted from that visit was just a small piece about the 'good, bad, and ugly eggs', and they used one of our tricolored pictures. Once something like that gets out in the media and is potentially interesting to the lay public, it just catalyzes interest from other journalists. So the next thing I knew we had a call from NBC news, the National Network and Robert Brazel's staff. His manager called and asked if they could come to do an interview. So they came out with this huge crew that we fit into our little microscope room, and while sitting at the microscope, we spent hours talking. The very last question they asked was "well, are you ready to do this on human eggs?" and I said "no, there are a lot of reasons why no patient would want us to dip their eggs in dye etc..", and the response was "OK, never mind". In my mind, it was better to just let it go rather than encourage them to extrapolate for what would have probably been hyped up for publicity. So it is A) a responsibility for scientists' training, and B) you need to remember that we are not trained to do this, so you need to rely sometimes on mentors' experiences or other people's experiences to figure out how to deal with a situation like that.

#### **When did you get interested to reach out to the public and communicate with it?**

This happened in the early to mid- 1980's as a member of the American Society for the Study of Cell Biology. I was on a committee that was charged with making cell biology research accessible to the lay public. There were 8-10 people on the committee, chaired by Bob Goldman. This public information committee was formed to respond to the fact that the media cannot understand the abstracts submitted to the conference. Thousands of abstracts were divided among all of us, with 100 per committee member. Each member was charged with the identification of ones that carried the most relevance to human health, and 10 abstracts were then selected. These were rewritten so that 8<sup>th</sup> or 10<sup>th</sup> graders could understand them, and a press book summary was then sent out to the media. This is a good example of what I did for 8 years, leading me to develop a knack for what is important and for asking questions about why humans should be interested. I was able to develop a skill set for translating science for public consumption, and I have used this exercise over the years with graduate and professional students.

I am a teacher always, and at Tufts I was in charge of a graduate program called "gap junction", funded on the belief that "communication is education". "Gap junction" was composed of a group of veterinary and graduate students that twice a year went out to local science fairs and served as judges in the late 80's and 90's. This was an outreach effort to help students learn to communicate. I have always considered communications as part of my responsibility, which includes a need to convey it to other students as well.

**You've been at the interface between the basic science and clinical applications of studies on oocyte development, never losing sight of the clinical applications, needs and practices. What led you to**

#### **doing so, and do you think that we are doing all that we can to translate findings between fields that may not always seem to move forward in sync?**

A place to start is a favorite story of mine is about the Krogh's principle, which was introduced to me on my first day of graduate school by Everett Anderson, my graduate mentor. At the time he was studying the ovaries of every kind of animal that you can think of, and he did much of the classical work on the ultrastructure of fertilization and early development. He really shared with me this Krogh's principle that said that for every question that you ask in biology, there is an organism uniquely suited to provide the answer. At the time he was still heavily involved in sea urchin research, but the NIH came down with a directive that said that we are no longer interested in these organisms that really had been the stuff of experimental embryologists for many years. He made the decision to move to the mouse; this was a huge transition, it meant developing new technology, really understanding the physiology of a mammal in the context of how the ovary worked. I remember that he was reluctant to do that, but it was the only way to sustain his NIH funding. So we made the shift in his lab- this was in the early 70's, I was probably a second year graduate student at that point. The momentum that resulted over the next 30 years is well known-in terms of mice -as we now have genetically tractable models that we can answer important questions with! To a certain degree-I often wonder if in adopting the mouse as a model for human diseases (and on a staggering financial scale), we have forgotten Krogh's principle by making tacit assumptions that this fuzzy test tube will really bring us to the next level of comprehension in reproductive science. For some aspects of clinical practice, it has paid off. Consider people like John Biggers who used the mouse to set the foundations for embryo culture media formulations used in human assisted reproductive technologies (ART) today.



**Fig. 2. Artist's rendition, commissioned by Dr. Betty Hay, on the occasion of Albertini's move from Harvard Medical School to Tufts showing Dr. Hay presenting Albertini with an inscribed Paul Revere bowl - the usual going away gift. Lab members, friends, and colleagues are depicted in prototypical poses and include Betty Hay, Everett Anderson, Dan Goodenough, and Rich Murphy.**

From the animal science and agricultural fields, many ART being used for humans were already being performed with domesticated animals. This is really what led me to appreciate the fact that while the mouse is a wonderful model for many basic questions that we were asking (like the GDF-9 story that turned out so interesting in itself), it really wasn't beneficial for the advancement of human ART. Case in point is embryo cryopreservation; it worked well in domesticated animals, so it quickly became adapted in human ART without "murine intervention". This led us to the point of where we are in the world of human oocyte cryopreservation as well. The point is that Krogh's principle kind of drifted into the background on an international scale- a bit too *mousocentric* for my liking. One of the causes that I have tried to champion is where do you draw the line between what is relevant in the studies of model organisms and the need to either tackle those questions in the species that you are interested in (*i.e.* the human or the cow) directly, or find the most appropriate model. From a career point of view, this is something that would frankly be a mistake for a young person since the funding system is so wedded to the idea that the mouse is a perfect model. Right now in the United States, one of the biggest impediments to really doing translational research for the human has been the 'mousephilic' focus on this organism. It was just a couple of years ago that Lou DePaolo at the NIH started this program, 'Dual Purpose with Dual Benefit', in other words "Can we get 2 for the price of 1?". Can we get people that are interested in the human biology and ART to work with animal scientists, finally? So there is some sign that this attitude and philosophy is turning around. But I think that it has been one of the struggles for many of us that have wanted to extend our basic research into a more clinical translational realm, and realized that there is a risk in that; from a resource point of view, we need a change in the philosophy of the NIH. That has been slow to come, very slow to come.

Of course in parallel now, we have to remember that we have the blossoming of molecular biology, in the early 1980's and we had the emergence of model systems biology. We saw this in the work that led to the Nobel prize for the cell cycle: the fly was on the map, the worm system came on the map, and *Xenopus* did its thing for the biochemistry of the cell cycle. There are unifying concepts that have been gained in the advancement of science that are due to using several model systems. Once the genomes are harvested, the next step can be taken. We now have genomes for so many animals. To me this opens up the doorway to go back to Krogh's principle. Now you can survey on a phylogenetic level fundamental processes in different organisms. There is a circular argument here, because having an open mind in the 19<sup>th</sup> century and early 20<sup>th</sup> century is what advanced the cause of science. Let's face it, that's what Darwin was thinking about; it was in the diversity of organisms. It was one of the reasons why August Krogh got the Nobel Prize in 1920 because he figured out how the circulatory system worked in frog skin. Now that we have the genomic tools, we can actually go back to more organisms and revisit Krogh's principle, as it relates not just to human biology but also environmental causes. You can

now begin to survey how a changing environment is influencing the health and productivity of contaminated saltwater marshes, just as one example.

You have to adapt to the reality of funding to sustain your research efforts, and yet I have not been willing to sacrifice all my principles given the changes in the funding landscape that I have witnessed over the years.

**It is unquestionable to anyone that knows you that you have fun doing basic science. Could you share a favorite memory of yours?**

The main thing that I've tried to bring not only to my trainees but also to the field is to begin bringing live cell behavior in what were very difficult model systems to do this in. One of the highlights was that we developed a live imaging system for detecting fluorescent molecules in living cells in the late 1970's. The first published picture of a tricolor fluorescent cell we published in the cover of *American Laboratory* in April of 1982 (Fig. 1). We were working with filter combinations that would allow us to detect different dyes not only in fixed cells but we were doing this in living cells. We built a system that had a gigantic video camera mounted on a Zeiss upright microscope that we bought from an astronomy company in upstate NY because at that time, it was sold only for use in space exploration. But it was low light level detection camera! Because of the size and weight of it, we even had to have an adapter engineered that would support this thing so we could fit an upright microscope under it (Fig. 1). This was accomplished by my very first postdoc, Brian Herman, and led to the development of a live imaging system capable of recording organelle movement in living cells. This was a classic paper that we published in the early 80's in the *Journal of Cell Biology*. The point is that I have really enjoyed bringing visualization of cell structure, not just to my field but also to bring technology to fields in general. The emphasis has always been dynamics of cell behavior - organelle movement, the



**Fig. 3.** Lab group at Tufts from the early 1990s showing from left to right, Britta Mattson, Carlos Plancha, David Albertini, Carlos' future wife, Susie Messinger, and Dineli Wickramasinghe.

cell cycle- and the thrill we obtained from seeing these events for the first time is something that I have always enjoyed sharing with others. However, it has been risky taking on challenges like this and getting buy-in from funding agencies or peers has not always been straightforward.

Fortunately, I have always had people willing to take chances with me and my crazy ideas. When we went to Tufts, we bought the first PC computers to try to do image analysis. This would have been 1984-1985, it cost us \$7000 dollars to buy our first IBM PC- but the problem was that there was no source code available for this kind of application. So, I just hired all these really bright Tufts undergraduates to come in and make it useable so we could in those days just capture images, pseudocolor images, measure intensity etc... It was at least 6 to 7 years before the first commercial products came out. I really loved being at the front edge of what we can do as technologies emerge and to apply them to the study of cell structure and function. This actually goes back to what I did for my PhD. I was an electron microscopist at a time when electron microscopy was still a new and powerful tool. I was enamored with the prospect of seeing things in ovaries and eggs that were not likely to have been seen before.

Back in those formative years, I first began to appreciate the notion that “chance visits the mind of the prepared” (Pasteur). And learning to take advantage of opportunities when they arise is something I have always encouraged my students to embrace, most certainly as a result of the chance events that I have experienced. A case in point harkens back to those early days of electron microscopy when I was a graduate student at Harvard Medical School. You could say this was the dawning of my interest in imaging technologies.

A new technique known as freeze-fracture electron microscopy was just emerging and one of the few machines available in the world at that time was located in the Anatomy Department. Dan Goodenough and Bernie Gilula, resident experts on this technology, were kind enough to take me under their wings and see that I acquired a level of expertise shared by few at the time. This method, which involved freezing, splitting, and shadowing the surfaces of cells or tissues, was the rage of the time because it provided a perspective of the inside of cellular membranes that had not yet been appreciated. Before I knew it, I was being sought after to aid many investigators in their research, and for my thesis studies I was able to publish several high profile papers that launched my fledgling career.

Take home message-I was in the right place at the right time. We captured the inside of membranes and I very much enjoyed sharing the technology with many others. I looked at samples with others, not just to teach them to take photos but also to bring them closer to my own excitement. My career contains a theme of jumping into a technology in its infancy and bringing it to an operational level that adds a new dimension to your field of interest, and makes a difference for those you share it with.

**You are now an Editor-in-Chief for the *Journal of Assisted Reproduction and Genetics (JARG)*. How do you see your career leading up to this role and in turn, where has it led you?**

There was indeed a reason why I took on this role. I actually started working with human oocytes for the first time with you and Catherine Racowsky at the Brigham and Women’s Hospital. This work has always been difficult to do in the US, and you had the



**Fig. 4. Lab group from the mid 1990s** with (from left to right) Alp Can, Ann Allworth, Mary Jo Carabatsos, Susie Messinger, David Albertini, and Raquell Holmes. Below, the dinner group from the days of the Albertini-Overstrom with the author (CC) seated at the end of the table.

willingness to take on Catherine’s collaboration as it turned out to be a ‘marriage made in heaven’ for the two of you. It was formally my first chance to do work with human oocytes and it allowed for a significant transition in my career. I haven’t looked back since then. I now have multiple collaborations with human IVF laboratories, many of which are overseas for practical reasons. My research has taken on a more translational direction, while it decreased my chances for funding from NIH. The ART community began noticing our research with human eggs and with it the opportunity to elevate the quality of research in reproductive medicine as treatment strategies for infertility continue to evolve. As my career has matured, I have had a growing interest in helping patients realize the opportunities of parenthood.

Over the last decade, I have had the chance to understand the mission of the American Society for Reproductive Medicine (ASRM) and what was needed to improve the perception and practice of Reproductive Endocrinology and Infertility (REI) in the US. It was in this context that the ASRM approached me in late 2008, in the spirit of making JARG a respected and informed journal that would bring breakthroughs in basic science to the forefront of human ART. My career reputation and tendency to foster discourse and discovery contributed to this opportunity to communicate the good, the bad, and the ugly side of reproductive medicine in a fast-changing world. The recent surging interest in the field of fertility preservation has created new avenues for research in reproductive biology and medicine that will have a long range impact that I see JARG con-

tributing to in the future. And to keep abreast of the need to train and guide the next generation of scientists and clinicians, I also anticipated that JARG would provide a training ground for nurturing our commitment to a bench-to-bedside paradigm consistent with the changing times.

To wit, one of the first things I implemented when assembling an editorial board of experts that would span the realms of basic and clinical ART was to engage many of the young physicians and scientists that I have met over the years. I love that I have a job that brings young people into my life. They have always been my extended academic family and now this is happening with physicians. Providing a structure, impetus, and set of standards for good writing and reviewing is one way an editor can reach out to and groom the next generation of reproductive scientists and clinicians.

#### Note by C. Combelles

As can be seen in this interview, David is an educator and his contributions are multi-faceted. He ensures that his still growing family of trainees is fully prepared to face the challenges ahead. David does not sit back or turn away from a problem or challenge; he speaks up and/or acts. I advise the reader to follow David's reflections and wisdoms through his regular editorial publications in JARG. The learning goes on for all of us and for our field at large!

#### Acknowledgements by David Albertini

It is difficult to thank all of the wonderful people who have influenced my journey through the wonders of oogenesis but foremost, my mentors deserve the bulk of the credit: Tony Mahowald, Arthur Hertig, Everett Anderson, Richard Berlin and John Biggers have all left a lasting impact on what has transpired over the past 40 years. I would also like to warmly thank my students, postdocs and research assistants with whom we have shared many laughs and a sense of accomplishment. And finally, my sincere thanks to the many colleagues and friends who have allowed me to enter their lives in a small way to benefit the health and well being of our children and theirs.

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