International Society for Hyaluronan Sciences

The Legacy of Endre A. Balazs, M.D.

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Cleveland, Ohio
BANDI TRIBUTES

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www.endreabalazsfoundation.org
Thank you for being here today to honor our friend and mentor, Bandi Balazs. And thank you Vince and Carol for arranging this special part of our meeting, and for the work you both have done to make this whole meeting possible, as well.

For full disclosure, credit to James Comey, and as Bandi’s representative: “Lordy, I hope I don’t hear the words ‘dalton’ and ‘hyaluronan’ in the same breath!”

Bandi was a scientist, teacher, entrepreneur and innovator – and many other things, but he loved being a neologist. Hyaluronan, hyalocytes, proteoglycan, NIF-NaHA, IF-NaHA, matrix engineering, Healon®, glycosaminoglycan, lots of “visco” words, and biomatrix (with a small b) (and NO, it is no longer “ground substance”, whatever new-ish term you choose to use).

His passion was hyaluronan, in whatever form, and his desire was to advance our relationship with his favorite molecule in basic science as well as medical applications. He was a “one man band” for many years, and one of his best achievements was the founding of ISHAS, giving all HA researchers a forum to share their ideas and facts and to stay connected through their worldwide organization.

Some secrets and applications of this ubiquitous molecule will remain to be discovered long after we are gone, but our contributions will be part of the “collective thinking about HA” forever.

Thank you, Bandi. And now four friends will share their impressions of Bandi. Always, Jenti
MY JOURNEY WITH BANDI TO ISHAS

Vincent C. Hascall, Ph.D.
Biomedical Engineering
Cleveland Clinic Lerner Research Institute
9500 Euclid Avenue
Cleveland, Ohio 44195
In 1999, I received a call from Glynn Phillips who I did not know at that time. He told me that he was organizing a hyaluronan conference to be held in Wales in 2000, and that the conference would honor Bandi during his 80th birthday year. He then asked me if I would be the Scientific Chair of the conference. I was surprised and also flattered. However, my response was that he should ask Torvard Laurent because Torvard was mentored by Bandi during Bandi’s time in Sweden after World War II. Glynn laughed and said that he had done so, but Torvard told him that I should do it. So I agreed, and my journey with Bandi began, for which I am eternally grateful.

The HA2000 meeting in Wrexham, Wales featured excellent talks for ongoing hyaluronan research, and provided a great opportunity to meet with HA centrics. It also had its funny moments, especially at the banquet in a nearby castle with medieval servants and lute players. As desserts were being served, Arnold Caplan stood to propose a nice toast to the Lord of the Castle (Bandi) and started by saying “It is great to be here in England”. Bandi was gracious in forgiving him.

Vanja and I had been invited to come to Bandi and Jenti’s Villa in St. Tropez after the meeting. What a marvelous place, and one that was a catalyst for bringing together members of the hyaluronan community for workshops, biographical sketches of hyaluronan researchers, and lots of fun. Thank you Jenti!

One of the first things Bandi said when we were settled in was “You and I are going to organize the next hyaluronan conference”. I agreed (who would not do so when Bandi decided). So HA2003 was in Cleveland and honored Torvard.
Bandi and I then worked on the two books that featured the presentations at the conference, which provided a nice summary of where hyaluronan research was at that time.

This is one of Bandi’s great legacies – his determination to provide a careful history of how the hyaluronan field started, how it grew throughout his lifetime, and the path for its continuation into the foreseeable future.

At the HA2003 meeting, Bandi and I discussed the meetings going forward, including ones abroad. I suggested that a meeting in Japan would be good, given the support of companies like Seikagaku and the strength of hyaluronan research in Japan. Bandi was a bit lukewarm about that, but changed his mind some time later. He sent a letter to Seikagaku outlining what he thought would be needed and how he could help if an international conference were to be held in Japan. Although he was trying to be facilitative, Seikagaku, perhaps from previous competitive interactions with Bandi, declined to participate.

When we discussed this, he felt that it would be a good idea to establish a Hyaluronan Society, which would have as its primary purpose ensuring the support for future hyaluronan conferences. He felt that this would make it clear to the industrial community that his involvement in promoting the conferences was not related to past potential competition from Biomatrix. Thus, the International Society for Hyaluronan Sciences (ISHAS) was born in 2005. Bandi was the Society President for the first 5 years, during which it blossomed and provided critical support for HA2007 in Charleston and HA2010 in Kyoto, Japan.

Sometime before the Society was formed, however, and shortly after Seikagaku declined to participate in supporting a hyaluronan conference in Japan, Seikagaku indicated to some of the hyaluronan community that it did plan to have a conference in Japan honoring Koji Kimata’s contributions to hyaluronan research. I became aware of this when Bandi, rather irritated about it, called me and felt we should not go. After the call, I sent an email to Seikagaku saying that it was very nice that they would honor Koji, but that his contribution was far greater than hyaluronan, and that a better title for the conference would be Koji Kimata’s contributions to Extracellular Matrix Biology. They agreed, and Bandi laughed and let me know that it would be OK if we went.
The outcome of this journey was that ISHAS was formed and able to support and facilitate the HA2010 conference in Kyoto, Japan with Koji as the Program Director. Very fittingly Bandi, in his 90th birthday year, was the conference honoree.

We will all miss Bandi very much and reminisce a lot with glasses of wine about our personal interactions with him and Jenti in St. Tropez, in New York, and at the remarkable HA conferences he created and inspired. I especially remember his sense of humor and the fun we had while he drove his small Smart car into the hills from St. Tropez.

There is no doubt that his legacy for promoting hyaluronan translational and basic science will continue long, long into the future, especially for his founding of ISHAS. However, those of us who had the privilege to interact with him as I did will also remember him as a warm and kind-hearted man with an infectious laugh as long as our memories last.
ENDRE A. BALAZS: THE INNOVATOR

Phil Band, Ph.D.
Professor
New York University
School of Medicine
301 E. 17th Street
New York, NY 10003
philip.band@NYUMC.org
I was asked to speak at today’s gathering about Dr. Endre Balazs as a businessman. Considering the financial success of the products he brought into the world, Bandi, as he was known to his friends and colleagues, certainly was as successful in the world of commerce as he was in the world of science. But as we all know, Bandi was much more than just a commercial success. He merged his business and scientific talents into a powerful persona, before it became stylish to do so. Bandi understood that financial independence was the only way to maintain scientific independence. His dual role as Chief Executive and Chief Scientific Officer of Biomatrix speaks volumes about the unique way he combined business and science throughout his career.

Instead of focusing on Bandi’s business accomplishments, I am entitling this short remembrance: “Endre A. Balazs, the Innovator”. Bandi was clearly more than a businessman, and more than what most people think of as a scientist. I am reminded of a quote from another refugee of the Second World War, Theodore Levitt, the economist and long-standing editor of the Harvard Business Review: “Creativity is thinking new things. Innovation is doing new things”. Bandi consistently and tirelessly took his creative ideas to the next stage, to innovation. He was driven by the need to methodically progress his ideas into products that served medicine, science and people. The negative reaction that often accompanies new ideas never deterred Bandi. He had the imagination to conceive of multiple new uses for hyaluronan, and the persistence and common sense needed to advance new concepts into medical reality. By now, hundreds of millions of patients have benefitted from the innovations that Bandi brought to medicine.

When Bandi first came upon hyaluronan as a young researcher in Theodor Huzella’s laboratory, his interests quickly transcended those of his fellow scientists.

From the beginning of his career, Bandi sought to find applications for hyaluronan’s fascinating physicochemical and biological properties. He was willing to go where no one had gone before. He started simply, in a way that would serve him well throughout his life. During the Second World War, Bandi identified a need for an egg white substitute (since one of his favorite desserts was meringues), quickly realized that synovial fluid had similar properties to egg white, and subsequently patented the use of synovial fluid from cattle as a substitute for egg white in baking and food preparation. The idea that synovial
fluid resembled egg white dated back several hundred years, to Paracelsus, who named synovial fluid because of this resemblance (syn ovum), with egg white. But until Bandi, no one thought to make this substitution in a practical way. Though not one of his best-known inventions, this story from Bandi’s early scientific career clearly portended Bandi’s unique ability to identify needs that hyaluronan could fill, and his drive to bring those applications to reality. To paraphrase Albert Szent-Györgyi, Bandi saw what others had seen, and thought what no one before had thought.

It was the need to fund science that brought out Bandi’s business skills. He was fond of a cartoon I kept on my wall which read: “the difference between a hypothesis and a fact is the amount of money that's gone into proving it”. But money is not enough. Bandi had a unique ability to inspire people around him with his vision.

His enthusiasm was infectious, as you will hear from other speakers today. He was especially good at focusing his creativity on problems that needed solving, and working with others to bring these ideas to life. When he purified and patented the first NIF-NaHA (non-inflammatory fraction of sodium hyaluronate), he had to transform from his professor persona, into a business persona in order to survive among the sharks of the pharmaceutical world. He
was a quick study when forced to swim among the sharks, and quickly learned to hold his own. He was always firm but fair, and successfully negotiated with companies hundreds of times the size of his own.

Bandi always pushed his own limits, and those of the people who worked with him. It wasn’t enough for Bandi to create the first medically useful hyaluronan preparation, including a way to specify its properties to ensure its safety. Another man might have stepped back and enjoyed the financial fruits of his labor, when Healon® transformed ophthalmic surgery and quickly became a commercial success. Not Bandi. Enabling the concept of viscosurgery to come to life was not an end game for Bandi. He often reminded me that he founded Biomatrix when he was 64, and that there was never an excuse for being too tired to work. The royalties he received for Healon helped Biomatrix survive and ultimately become a leader in developing the multiple applications of hyaluronan that now exist in medicine. Researchers had crosslinked hyaluronan more than 20 years before the founding of Biomatrix, but it was Bandi who recognized that crosslinking was the way to control the residence time of parenteral hyaluronan in tissues and its physical form. It was Bandi who dedicated Biomatrix to fulfilling his dream of customizing the hyaluronan molecule for specific medical applications. Other biopolymer companies took synthetic polymers with the desired characteristics, and chemically modified them in an attempt to make them biocompatible. Bandi took the opposite approach. He believed everything should start with hyaluronan, the most biocompatible polymer known to medicine, and from that starting point we could invent ways to chemically modify hyaluronan to create the physical forms and residence times needed for new medical applications. This opened entirely new vistas for hyaluronan in medicine, and to this day remains a fundamental scientific principle directing efforts to develop new and better hyaluronan-based products.
I don’t know if Bandi was an admirer of Thomas Edison, but Bandi taught me many of the lessons that Thomas Edison was famous for. “I never did a day’s work in my life. It was all fun…”. For Bandi, work, science and life were a continuum, and he made this clear to everyone in his inner circle. Bandi often said to me “I get enough exercise by walking all day from one laboratory table to another”. This is likewise a well-known Edison quote. Bandi and Edison had a common work ethic, unending energy and boundless enthusiasm for their work. They were driven to bring new innovations to life. In Bandi’s life, this work devotion was single-mindedly directed at a molecule, hyaluronan. Bandi certainly got more out of hyaluronan than anyone ever expected. He contributed his entire scientific and business career to the elevation of hyaluronan from “ground substance”, to the medically and biologically important molecule we now know it to be.

I’d like to end with a few Bandi quotes that I have always remembered, and which very much guided my own career, in science and in life.

- “When in doubt, leave it out”: Essential to having publications you can stand by through the decades.

- “Never make decisions until you have to”: A temptation I personally still struggle with to this day.

- “Scientific presentations must be humble, presenting hard data, maybe suggesting a hypothesis, but always in a way that allows your audience to draw their own conclusions, not necessarily the same as yours”.

- “Marketing presentations are the opposite. Your primary goal must be to make it easy for your audience to understand the financial potential of your vision, to help them adopt your vision, and to take on the challenge”.

Bandi was a true innovator, in every sense of the word. He was a trusted friend and collaborator to many in this audience. But most importantly, Bandi maintained his humanity through all his scientific and business endeavors. Science, business, and love were merged into a powerful life. It was both our honor and our pleasure to go along with Bandi for the ride.
ENDRE A. BALAZS
A DISTINGUISHED SCIENTIST

Carlos Belmonte, M.D., Ph.D.
Professor Emeritus
Instituto de Neurociencias
Universidad Miguel Hernandez-CSIC
03550 San Juan de Alicante
Spain
Endre Balazs (Bandi) was an exceptional man. The picture of the varied, salient facets of his rich personality offered by the previous speakers, largely justifies applying this adjective to describe him. Nonetheless, the extraordinary success of Bandi as a visionary entrepreneur, capable of transforming his dream of developing new medical therapies into reality, perhaps obscured the importance of his research contributions. These focused on identifying the biological mechanisms underlying the therapies that he discovered, developed and applied for medical treatments. His work on characterizing mechanistically the action of hyaluronan (HA) on pain was an important part of a research effort that he never interrupted, and in fact maintained with passion literally until the final days of his life.

The main objective of Bandi’s research work was to identify the cellular and molecular processes whereby hyaluronan, the enigmatic molecule that captured his interest for more than seven decades, exerted its biological functions. I was lucky enough to accompany Bandi along 30 years of that intellectual endeavor, during which time we formed a somewhat odd scientific couple composed of a molecular biochemist and a systems neurophysiologist, whose common scientific interests may appear at a first glance, very far apart.

I first met Bandi and Janet (Jenti) Denlinger -- his lifelong scientific and personal partner -- in 1980 in NY at the 4th Congress of the International Society for Eye Research (ISER) that Bandi had founded and chaired. My interest during this time was to use the cornea of the eye as a simple and accessible model to analyze the activity of sensory nerve endings detecting pain stimuli electrophysiologically. We soon noticed the similarity of our views about science, basic research in medicine, personal life and many other aspects of human nature and culture. Bandi and Jenti convinced me to get involved in ISER, and during the following four years, we jointly organized the VI ISER Congress in Alicante, Spain, and meanwhile became close friends. Since then, my affection and admiration for Bandi grew continuously, the result of hours and days of research planning and endless discussions about science and life.

In the early eighties, Bandi and Jenti were starting the Biomatrix adventure, scientifically supported by their seminal experiments showing that intra-articular injection of cross-linked high molecular weight (HMW) HA reduced pain in inflamed knee joints of horses and humans. This observation prompted them to propose that in healthy joints, HA exerts a viscoelastic filtering effect. It acts as a shock absorber that decelerates the inertial mechanical forces transmitted to pain nerve endings during joint movements,
thereby reducing their excitation below the level required to elicit pain. Nonetheless, at that time, this hypothesis was not easily accepted. Other authors either denied the analgesic action of HA or suggested that this could be the result of the neutralization or dilution of inflammatory mediators by the injected HA. As a peripheral pain electrophysiologist, I suggested an objective way of proving a direct action of HA on pain nerve endings, that is, the recording of their electrical activity in response to movement before and after HA injection.

Bandi, always very persuasive, convinced me to do the experiments to test the elastoviscous filtering hypothesis of HA. In 1986, taking advantage of the sabbatical year that I was enjoying in Harvard and Utah, I started single nerve fiber recording experiments in the cat knee joint in vivo, a work sponsored by Biomatrix. Much to our surprise and excitement, intraarticular injection of hylan A, the 0.8%, 5 million MW (molecular weight), cross-linked hyaluronan prepared by Biomatrix, slowly attenuated nerve impulse discharges evoked by controlled joint movements in intact joints (Figure 1). Thus, we decided to continue and extend these studies in my laboratory in Alicante, where we analyzed in more detail how HA solutions of different concentrations, average molecular weights, and crosslinking characteristics affected nerve impulse activity in mechanically-activated joint sensory fibers. This group is still active today.
Figure 1. Effect of intra-articular injection of elastoviscous hylan on single-fiber activity evoked by passive non-noxious movements of the inflamed joint. A and B show an example of the mean impulse discharge of a joint nerve fiber evoked by three successive extensions of the joint before (A) and 1 h after (B) intra-articular injection of elastoviscous HA. C. Mean frequency values of movement-evoked discharges of eight individual fibers, before and 1 h after injection of HA. D. Response evoked by passive movement after injection of elastoviscous hylan expressed as percentage of the preinjection frequency value (**p<0.01, Wilcoxon test) (Pozo et al. 1997)
We published our first paper in Experimental Brain Research in 1997. From 2002 to 2011 we confirmed the attenuating effect of HA on impulse firing of pain nerve fibers evoked by innocuous and noxious rotations of the knee joint in different models of joint inflammation in the cat, rat and guinea pig. We demonstrated also that this action was more pronounced when the MW of HA increased, being absent with HA solutions of low molecular weight and elastoviscosity. Altogether, these data, published in the Journal of Physiology, Pain, Arthritis and Rheumatology, and Osteoarthritis and Cartilage, provided the first direct experimental evidence that intraarticular HA acts as an effective elastoviscous filter to attenuate the mechanical forces transmitted to pain nerve endings during joint movements, an effect attributable to the unique rheological properties of HA. When the elastoviscosity of HA was modified by dilution and/or breaking down of HA molecules, as occurs during joint inflammation, the buffering effect of HA on transmitted mechanical forces decreased, and joint pain fibers were strongly stimulated, evoking pain. Hence, our studies offered a first scientific explanation for the beneficial effects of intraarticular injection of HA on joint pain in osteoarthritis, and provided experimental legitimacy to this therapeutic approach in humans, named viscosupplementation by Denlinger and Balazs, and still used today as one of the leading therapies to treat OA pain.

In parallel, we tried to define, at the molecular level, how HA decreased nerve impulse activity in synovial nociceptor nerve endings, exploring the hypothesis that this was due to a reduction by HA of the opening probability of mechanically-activated (MS) ion channels expressed by joint sensory neurons. Although in those days the presence of MS channels in mammalian mechanosensory nerve endings was still hypothetical, their existence and biophysical properties were established in the cell membrane of frog oocytes.
Figure 2. A. Cell-attached recordings in oocytes with increasing negative pressure values, showing the relationship between the negative pressure in the pipette and the opening probability of SA channels. B. Effect of different elastoviscous solutions on intensity–response curves recorded in saline solution (filled circles); in the presence of 6 M MW HA (open squares); HA 96,000 MW (open circles), and Synvisc (open triangles). C. Diagram of the chamber employed to expose isolated membrane patches to saline or HA solutions, which were placed in two compartments separated by a central smaller compartment filled with mineral oil. The pipette with the attached membrane patch was moved from one compartment to the other through the oil compartment (arrow). Right, the response of a membrane patch to a negative pressure ramp in the cell-attached configuration, prior to the excision of the patch. Below, upper traces, recording of the channel opening activity induced by negative pressure in the same patch after excision. Compartments (a) and (b) were filled with saline solution. Middle traces, stretch-activated channel opening induced by negative pressure when the excised patch was immersed in saline solution (left trace) and Synvisc (right trace). No activity was observed in the presence of Synvisc despite the larger negative pressure applied. Lower traces, response to negative pressure in the presence of saline solution (left trace) and of HA 96,000 average MW (right trace).
Thus, we developed a preparation in which the electrical activity associated with the opening-closing activity of MS channels evoked by pressure was recorded in the membrane of Xenopus laevis oocytes, using patch-clamp techniques in both intact cells and in excised membrane patches. Our results showed clearly that the magnitude of the currents in whole cells and in isolated membrane patches elicited by membrane stretch was reduced when the membrane had been bathed in high molecular weight HA (Synvisc®) but not in low molecular weight HA, strongly suggesting that mechanical forces were less effectively transmitted to mechanosensory transducing channels when these were surrounded by large HA molecules. Thus, these experiments showed that HA acted as a mechanical stabilizer of the cell membrane channels expressed by joint sensory neurons.

The next step in the elucidation of how HA interacts with the membrane of nociceptor joint fibers was to explore whether HA molecules changed the activity of TRPV1, a non-selective cationic ion channel, which is opened directly or indirectly by protons, heat and several endogenous inflammatory mediators, thus behaving as the common path for the excitation and sensitization of polymodal nociceptor neurons. Using recombinant systems, mouse-cultured dorsal root ganglia (DRG) neurons and *in vivo* experiments, we found that HA also modulates TRPV1, by diminishing heat, pH, and bradykinin responses, and reducing the opening probability of the channel by stabilizing its closed state. In DRG neurons, HA decreases TRPV1-mediated impulse firing and channel sensitization by bradykinin. Moreover, intraarticular injection of HA in rats decreased capsaicin joint nociceptor fibre discharge. Collectively, these results indicate that extracellular HA reduces the excitability of the ubiquitous TRPV1 channel, thereby lowering impulse activity in the peripheral nociceptor endings underlying pain. Other TRP channels like TRPA1, were not affected by HA. Next, we modeled the interaction of TRPV1 with hyaluronan and found that the preferred location for putative HA binding in TRPV1 is a patch of positively charged amino acids located in its extracellular S5-pore helix loop. The polymer, by immobilizing this outer pore loop, obstructs the conformational change necessary to open the external gate, thereby locking the channel in the closed state. This work demonstrated that in addition to mechanical filtering, synovial fluid HA may play additional roles in the modulation of joint nociceptor fiber activity during joint inflammation.
Figure 3. TRPV1 channel model inserted in a lipid bilayer. The proteins are drawn as a ribbon and colored differently for each subunit. The cytosolic C and N termini have been removed for simplicity. The black square delimits the extracellular loops of TRPV1 and the docked HA. Hyaluronan tetrasaccharide is drawn as sticks and colored in pastel pink. The numbers indicate the sugar rings, starting from the non-reducing end. The loop side chains involved in the interaction are shown as sticks and colored accordingly to the color of its subunit. The dotted lines in red denote hydrogen bonds between atoms closer than 3.2 Å.
Figure 4. Joints are innervated by nerve endings expressing TRPV1 channels (upper panels). As shown in the lower panel, increase in the density of HA molecules interacting with the TRPV1 channel reduces its opening probability, as shown in the single-channel activity recordings, thereby decreasing nerve impulse activity in nociceptor endings.

This was the last paper authored by Bandi Balazs that appeared in Nature Communications just one week after his death. He did not have the time to participate in the writing and publication of the paper reporting a new HA formulation, with particular rheological properties and significantly higher inhibitory potency on joint pain nerve activity and nociceptive responses in animal experiments.

Bandi Balazs will be remembered not only for his contributions to ameliorate human health, but also by his fellow scientists as the researcher who made key discoveries for the understanding of how hyaluronan modulates sensory information associated with joint movements in health and disease. Those of us who were also Bandi’s friends will always miss his company and the mixture of powerful intelligence, humanity and affection that made him a very unique and complete person.
ENDRE BALAZS: SCIENTIST, PHYSICIAN, HUMANITARIAN

Charles Weiss, M.D.
Chairman Emeritus
Department of Orthopaedics and Rehabilitation
Mt. Sinai Medical Center
Miami Beach, Florida 33140
We are here today because Bandi has significantly affected each of our lives: from predicting virtually every line of scientific inquiry, medical and commercial use of hyaluronan decades before their realization, to bringing together an incredibly diverse group of scientists, physicians, academics and industrialists by founding The International Society of Hyaluronan Sciences (ISHAS) to advance and perpetuate the knowledge and utilization of this ubiquitous molecule. In this talk, I can only touch briefly on a few of his many contributions and, rather than specifically detailing each of these, will focus on his personal attributes of intellect, insight, commitment, motivation, courage, and character that helped make them possible.

I met Bandi and Dr. Janet Denlinger (Jenti) in 1973. I was on the full-time faculty of the Massachusetts General Hospital (MGH) department of Orthopaedics. Bandi was Director of Research at the Retina Institute he helped found, conducting multidisciplinary research with Jenti on the vitreus and hyaluronan in the Connective Tissue Research laboratory he developed. He had also established Biotriics, Inc., a company he formed to purify hyaluronan so it could be utilized safely in medicine.

In 1969 Arthur Helfet, Orthopaedic Department Chair at Einstein University in New York City, had used Bandi’s first non-inflammatory fraction of sodium hyaluronate (NIF-NaHA Healon®), in patients with arthritic joints. He was impressed with its safety and results, and encouraged Bandi and me to work together. During our initial meeting, I asked Bandi if he would speculate on the composition of fine fibers and filamentous fibrils that I found covering the surface and in the extracellular matrix of human articular cartilage. He referred me to his 1966 article with Bloom and Swann on the ultrastructure of bovine articular cartilage before and after treatment with hyaluronidase, and was certain that these fibers were hyaluronan. In 1937 when Bandi started medical school in Budapest, Theodor Huzella, Chairman of the Department of Histology and Embryology, asked him to investigate the argyrophilic fibers that surrounded cells. Huzella felt that these fibers formed an extracellular elasto-mechanical protective barrier. Within two years Bandi had determined that these fibers were hyaluronic acid, which Karl Meyer had recently purified and named. This started Bandi’s lifelong dedication to the science and medical applications of hyaluronan. He then gave me a hyaluronan tutorial outlining the location, structure, physiochemistry, rheology, bio-mechanical protective properties; as well as its effect on cellular mitosis, migration, and synthesis, as the “DNA” of the extracellular matrix, which he liked to call the biomatrix. When he was reasonably certain that I understood the “biology” of
the molecule he described to me how those properties could be used to relieve pain and improve function in arthritic joints. In 1945, Bandi predicted, based on his work on dog joints, that hyaluronan would be useful in preventing joint pain and ankylosis after trauma, infection, arthrotomy and arthroplasty. He later demonstrated that hyaluronan could decrease traumatic and postoperative scarring, diminish local tissue reaction to implanted foreign bodies, and protect delicate cells, membranes and connective tissue surfaces from mechanical, chemical and oxidative trauma. I was excited by the concept of using this ubiquitous molecule to address so many clinical problems. Bandi also gave me a copy of his “Blue Book” that contained the studies which supported these uses. When we next met, I asked him if he would present his concepts to our Orthopedic Arthritis Group at Massachusetts General Hospital (MGH) and if I could test Healon® on a surgical model. Bandi thought that, because his ideas differed so radically from the current concepts of arthritis treatment, they would not be accepted. Eventually he agreed to present his work. Of course, he was correct and none of his concepts were accepted. Intuitively I knew he was right and asked my department chair if I could do an experiment to determine if NIF-NaHA could diminish tendon adhesions after surgery: he refused. I then left my lab at MGH and began working with Jenti on reducing tendon adhesions after surgical repair in primates. In my clinical practice Bandi and I set up the first FDA approved blinded study of a viscosupplement (a term Jenti coined) for the treatment of arthritis of the knee. At this time, Pharmacia began manufacturing Healon for veterinary use after Bandi had demonstrated its efficacy for the treatment of arthritis in race horses and for detached retina in humans. In the early 70s Bandi suggested that Healon could be used to protect the corneal epithelium during lens implant surgery, and in 1977 ophthalmologic surgeons David Miller and Robert Stegmann began using it. This treatment revolutionized lens implant surgery and introduced the world to viscosurgery.

On March 24, 1977, our successful clinical trial at MGH (“A Clinical Study of Intraarticular Injection of Healon In the Treatment of Human Knees” IND12-814) was presented to the FDA. Despite successful studies in the US and Europe and the subsequent commercial success of low molecular weight “copies” of his original product in Japan and Italy, Bandi was dissatisfied. He felt that, since the elastoviscous properties of synovial fluid decreased in arthritic joints and clinical trials in race horse arthritis were much more
successful than those in humans, a higher average molecular weight hyaluronan, one which duplicated the rheological properties of normal young adult synovial fluid, was required. When Pharmacia did not pursue the intraarticular use of Healon in humans, Bandi and Jenti started Biomatrix to develop more effective hyaluronans for therapeutic use. In 1983 they developed hylan B gel for tissue augmentation and in 1984 hylan A, a high molecular weight hyaluronan solution. During the 1980s Bandi, Jenti and I continued to do both animal experiments and human trials to assure the safety and improved efficacy of hylans as antiadhesion and surface protection devices as well as viscosupplements. A mixture of hylan A and hylan B (hylan G-F 20) became Synvisc® which was approved in 1997 by the FDA along with Fidia’s Hyalgan (a low molecular weight hyaluronan) as the first viscosupplementation products in the US, 20 years after our first FDA application. Synvisc became the market leader for the next 20 years; however, Bandi continued to attempt to find even more effective devices, as you heard from Carlos Belmonte.

At this point I would like to address Bandi the Humanitarian:

- Not in the sense of philanthropy, as in funding chairs or lectureships at prestigious research universities such as the Karolinska;
- Not in the sense of establishing and funding not-for-profit research institutes and foundations such as the Matrix Biology Institute, the Retina Foundation, Boston Biomedical Research Institute, or the Balazs Foundation;
- Not in the sense of funding, equipping, and providing trained research personnel to do both basic and translational research, as was done at Columbia University and New York University;
- Not in the sense of founding not-for-profit international scientific societies and journals such as ISHAS, or The International Society for Eye Research (ISER) and its journal: Experimental Eye Research;
- Not in the sense of his support for the arts such as the Metropolitan Opera;
- Not in the sense of his commitments of time, advice and money to friends in need;

but something else. Something he did voluntarily, something which placed him at odds with most of those around him -- professors, colleagues, friends,
even family. One which placed his life and those closest to him in mortal danger, not just once, but every second of every day for almost a year at a time in his life when he had just begun his research, when he received his first hyaluronan patent, when he had just turned 24. Something he kept from me for the first 23 years of our friendship. Something I only learned at the Wenner-Gren Center in 1996 when a senior scientist at the Karolinska spoke at a dinner honoring Bandi’s scientific contributions.

On March 19, 1944, Germany invaded Budapest. Bandi had just finished medical school and was appointed Director of Infectious Diseases at the Military Hospital in Budapest, despite having no experience in that field. He was assigned to treat only Nazi officers. The “Jewish Laws” were in place. Jews were not allowed to attend universities, teach or enter any profession. Hungary had joined the war as an Axis nation and joined Germany invading the Soviet Union. Germany invaded Hungary when they discovered that the Hungarian Nobel laureate, Albert Szent-Györgyi, under the guise of lecturing in Cairo, was, on behalf of the Hungarian government, attempting to make an alliance with the Allies. Bandi’s most respected professor, Theodor Huzella, Chairman of the Department of Histology and Embryology, often spoke out against the anti-Jewish laws and allowed Jewish “students” to audit his classes. In April of 1944, under the direction of Adolf Eichmann, the Nazis began to implement the “final solution” for Jews in Hungary. Between May first and July fifteenth, 435,000 Jews in Budapest were rounded up and murdered. Although the rate of murders and train shipments to Auschwitz slowed, they continued until February 25, 1945 when the Soviets drove the Nazis from Budapest.

During this time a young undergraduate student, 5 years Bandi’s junior, Eva Fisher, daughter of a prominent Budapest Jewish family, sought refuge in the basement of an unused histology building. A small group of medical students and doctors, Bandi among them, protected, fed, clothed and gave her medical care. On one occasion Eva had to change locations. Bandi accompanied her and they were stopped by a Nazi officer. Although Bandi had the requisite papers, Eva, of course, had none. If caught they would be arrested, killed and their friends and families imperiled. But Bandi, with his unique ability to read people, joked with the officer and distracted him to the point where he neglected to check their papers and allowed them to pass.

Eva Fisher, now Professor Eva Klein, is an internationally renowned scientist who discovered the role of the Epstein-Barr virus in Burkett’s Lymphoma and found that a unique type of lymphocyte, which she named “killer cells”, had the ability to kill cancer cells infected with viruses. In 1975, she was
recognized by the U.S. Cancer Research Institute as one of the founders of the field of cancer immunology. Her research has helped save thousands of lives. It has been said that: “he who has saved one life it is as if he has saved the entire world”¹. Bandi was the literal embodiment of this concept.

In conclusion, Bandi’s life, his actions and accomplishments, reflected the highest ideals of his profession and moral commitments. As a scientist, to paraphrase Szent-Györgyi²: “he saw what others had seen but thought what others had not” utilizing virtually every tool and discipline known to science to define the structure, function and application of the hyaluronan molecule. As a physician Bandi’s concepts of treating disease mirror those of Hippocrates: physicians treating disease have had two principle objectives: to do good and to do no harm³. The use of Healon in the anterior chamber of the eye has changed lens implant surgery from a difficult, time-consuming procedure with a significant risk of corneal injury, to a safe, routine procedure that has benefitted more than 360 million patients worldwide. This year alone hyaluronan will be used in more than 3.5 million intra-ocular procedures in U.S. and 20 million worldwide.

The treatment of arthritis by viscosupplementation is also reflective of this concept. The surgical treatment of arthritis of the knee in the U.S. last year resulted in over 10,000 deaths and permanent impairments directly related to this treatment, while the use of NSAIDs for arthritis resulted in more than 12,000 deaths for this non-lethal disease in the U.S. last year. It has been estimated that worldwide over 80 million patients have been treated with safe and effective viscosupplements for arthritic joints.

Finally, we come to Bandi the Humanitarian. By dint of his intellect, insight into people and science, the courage to move and to standup for his convictions in science, politics, and morality, the lives of virtually hundreds of millions of people have been saved and enriched.

¹ Talmud
³ Hippocrates: The Epidemics