# A Conversation Between Stefano Buono and Ken Herrmann

Stefano Buono[1] and Ken Herrmann[2]

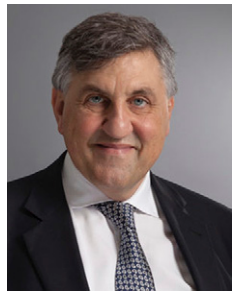
[1]*Elysia Capital LTD, London, UK; and* [2]*Universitätsklinikum Essen, Essen, Germany*

Johannes Czernin, editor in chief of *The Journal of Nuclear Medicine,* recently initiated a series of recorded discussions with leaders in nuclear medicine and molecular imaging. This month he asked Ken Herrmann, a professor of nuclear medicine at the Universitätsklinikum Essen (Germany), to talk with Stefano Buono, an accomplished Italian physicist and alumnus of the European Organization for Nuclear Research (CERN). He is widely known as the founding leader of Advanced Accelerator Applications (AAA), an international radiopharmaceutical company, where he served as chief executive officer and board member. He received his master's degree in physics from the University of Turin in 1991 and went on to work for 10 y with physics Nobel laureate Carlo Rubbia at CERN. While there, Buono actively participated in the development of CERN's Adiabatic Resonance Crossing method. He also worked with the Centre for Advanced Studies, Research and Development in Sardinia. There he headed a team of engineers working on international research projects in the field of energy production and nuclear waste transmutation. After founding AAA in 2002, he guided the company's success in developing, producing, and commercializing molecular and nuclear medicine diagnostic and therapeutic products. The company was acquired by Novartis in 2018, and Mr. Buono remains a consultant. He also serves as chair of the board of directors for LIFTT srl, dedicated to stimulating technology transfer from academic institutions to industry, and as chair of the board of Planet Smart City, dedicated to solutions and innovations in affordable and sustainable housing. Mr. Buono also serves as founding Chair of Elysia Capital LTD., a single-family office focused on development of projects contributing to innovation, social impact, well-being, education, art, and culture.

***Dr. Herrmann:*** *Stefano, thank you for agreeing to be interviewed for* JNM. *Please tell us a little bit about your background and career.*

**Mr. Buono:** I am a physicist by training and never worked in the field of medicine. I worked at CERN on a high-energy-field project trying to use a particle accelerator and subcritical reactor to create energy by destroying nuclear waste. This was in the lab of Nobel laureate Carlo Rubbia. A patent was developed around the manufacture of isotopes using a particle accelerator, with potential application in nuclear medicine. In 2002, I decided to start a company trying to develop this patent, and Carlo Rubbia was very supportive. This was the start of AAA. While I never ended up capitalizing on the patent, the circumstances provided me with the opportunity to explore unmet needs in the field of nuclear medicine.

At that time, European authorities were requiring production of FDG for PET under Good Manufacturing Practice (GMP), which was a major limitation for hospitals. I saw this as an excellent opportunity to establish commercial radiopharmacies, register FDG as a drug, and distribute it over larger territories. Over the next 15 y, we established a network of 20 manufacturing facilities in 8 countries in Europe, as well as the United States and Israel. We grew from zero to 630 employees. This was quite a big growth story, but it was also very intense. Over the course of our history, we analyzed around 200 different business development opportunities. Some of them translated into licenses and others into acquisitions. Overall, we completed 13 acquisitions during that time period, further complementing our organic growth.



**Stefano Buono**

***Dr. Herrmann:*** *Let me follow up on the radiopharmacies. How did you develop AAA?*

**Mr. Buono:** We started in France, very near the CERN and then expanded to Italy. Our original intent was to focus on drug development, but we saw the business opportunity for FDG and thought it made sense to first establish our capabilities in diagnostics. We were encouraged to build a facility in the north of France, and then we continued to expand our territory into Spain and later into Portugal and Germany, following the footprint of FDG.

***Dr. Herrmann:*** *Obviously the most known story and the biggest accomplishment of AAA is the Lutathera story. You mentioned before that you were looking at around 200 different business development opportunities. How and why did you prioritize peptide-receptor radionuclide therapy (PRRT) and* $^{177}$*Lu-DOTATATE (Lutathera)?*

**Mr. Buono:** This story began back in 2006, when I started thinking that if you can reach a target so effectively with a diagnostic drug, why can't you attach a particle emitting isotope to treat the target? I later realized this concept was not new—radioiodine had been around since the 1940s and other drugs were being used in research. For example, I observed the use of lutetium-labeled DOTATATE and DOTATOC at the European Institute of Oncology (IEO). The pharmacist from IEO, Giovanni Tesoriere, came to work for AAA in 2004 and immediately suggested that we change how these drugs were manufactured to make a ready-to-use formulation that could be injected immediately. To enable centralized manufacturing and shipping to other locations, we also had to create a more stable solution that could last a few days.

We started concentrating our attention on another compound being used in clinics, $^{90}$Y-DOTATOC, since it appeared that there would be an opportunity to capitalize on an expiration of the intellectual property. Unfortunately (or maybe fortunately for us in the end), another company licensed the compound and we had to abandon this

strategy. We then decided to focus on lutetium-labeled DOTATATE, which had been licensed to a small U.S. company called Biosynthema. One year later, in 2010, we acquired the company and the global rights to the drug that we eventually developed into Lutathera. It took us 8 y from that acquisition to complete development and GMP manufacturing, to run a multicenter phase 3 pivotal study, to submit a full regulatory package, and to achieve to approval in Europe and the United States. It seemed to go by much faster, due to the intensity of the work!

In the meantime, we built a pipeline of theranostic pairings and expanded our global footprint, mostly from the 200 business development opportunities. We also listed AAA on the NASDAQ stock exchange in November 2015, which was a colossal undertaking.

***Dr. Herrmann:*** *What are other examples of the pipeline you mentioned?*

**Mr. Buono:** We in-licensed PSMA-R[2], a urea-based ligand that targets prostate-specific membrane antigen expressed on most prostate cancer cells. Another compound in the pipeline is NeoB, a gastrin-releasing peptide receptor antagonist. Last, there is an agent targeting 2 subtypes of integrin receptors. These deals all took a lot of time and effort to execute.

***Dr. Herrmann:*** *That's important that you mention this: it really takes persistence. What were the biggest challenges and the most important lessons you learned during the 12 y between 2006, when you first started thinking about entering the therapeutic space, and 2018, when Lutathera became an FDA (Food and Drug Administration)-approved drug?*

**Mr. Buono:** Overall, I would say that the most difficult part was to find a good drug candidate. After that we faced many challenges, but I cannot say that one challenge was necessarily bigger than another. The entire development process was very complex. But step by step, year by year, we stayed the course and were convinced that we would eventually succeed.

***Dr. Herrmann:*** *How did you navigate the regulatory challenges in developing a therapeutic versus a diagnostic agent, and how did you educate nuclear medicine physicians?*

**Mr. Buono:** The most critical aspect of our regulatory success was that we decided to follow a traditional pharmaceutical approach that was not very common in the nuclear medicine industry. The only other example was the big clinical trial that Algeta/Bayer ran for $^{223}$Ra-dichloride (Xofigo). We followed this example and didn't try any shortcuts. This was really the key, not only for obtaining registration, but also to bring nuclear medicine into the pharmaceutical world. We accepted the challenge to design a large phase 3 study. This prospective randomized trial was also absolutely mandatory to convince the FDA and oncologists.

The other significant factor was to simplify the preparation of the drug. Nuclear medicine has always been perceived as a very complicated field by oncologists. We saw this issue adversely impact the success of other nuclear medicine drugs in the marketplace. Our goal was to make the preparation for administration as simple as performing chemotherapy. We also believed that if we could establish Lutathera administration as an outpatient procedure everywhere then we had a good chance for this nuclear medicine drug to compete on an equal footing with other cancer drugs.

***Dr. Herrmann:*** *How did you do this? How did you simplify the preparation and administration?*

**Mr. Buono:** There were 2 primary focus points. We formulated the drug to be ready-to-use, eliminating the need for onsite nuclear medicine laboratories. We also abandoned the long-standing nuclear medicine practice of using dosimetry to create individualized dosing for each patient, which is fascinating from a scientific point of view but very difficult to implement in a practical sense. We believed incorporating such an approach would have been counterproductive from both a regulatory and commercial launch perspective. I truly believe that the nuclear medicine industry needs to simplify how drugs are used if we want this field to have continued commercial success.

Another key learning point for us was the importance of reimbursement strategy and the ways in which this may impact the use or competitive positioning of a drug. This was an entirely new discipline for our industry.

Of course, all of these lessons and improvements are meaningless without reliability of manufacturing. This is key! Fortunately, we started to manufacture FDG in 2004, so by the time we were developing Lutathera, we had accumulated an incredibly strong knowledge base regarding both manufacturing and distribution. This expertise was invaluable when it came to distributing products within a few short days from production sites in Italy to administration sites thousands of miles away in Los Angeles or even in Japan. Reliability is key for patients.

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***Dr. Herrmann:*** *You had the huge advantage of having a lot of data early on. On the other hand, compounding is also a challenge as you now have to compete with these sites once you launch the product. So from your point of view is compounding more of an opportunity for developing drugs quickly or rather a challenge?*

**Mr. Buono:** I see compounding as both an opportunity and a challenge. In an ideal world, a nuclear medicine department should have the freedom to compound a drug for investigational purposes, but once it is approved and available under commercial-grade manufacturing, which is overseen by regulatory agencies, this practice should cease. This is the way the laws are written in many countries, as this approach helps ensure the highest levels of consistent quality and safety for patients. Such compounding practices were originally also very challenging with FDG; however, we succeeded because of our reliability. Little by little, many institutions realized that it was not worth the effort or expense to compound, once GMP was enforced.

***Dr. Herrmann:*** *You mentioned the differences between diagnostics and therapeutics. There are very few companies who really have expertise in both fields. Can you elaborate on the differences between developing a diagnostic and a therapeutic toward FDA approval, especially regarding financial and logistic considerations?*

**Mr. Buono:** From a technical perspective, there are few differences in the development requirements for regulatory approval of a diagnostic drug in comparison to a therapeutic drug. However, from a practical perspective, many additional challenges are involved in developing a therapeutic. The single biggest difference

between a diagnostic and therapeutic is toxicity. The very nature of a therapeutic includes an element of toxicity in order for it to be effective, versus the vast majority of nuclear medicine diagnostics that rarely carry any toxicity. Accordingly, you could group phase 1 and phase 2 diagnostic studies together and eliminate the need for larger phase 3 therapeutic studies, which are testing safety in significantly diverse populations alongside efficacy against a comparator. As a result of these larger and more complex studies requiring a comparator, therapeutic trials are by nature also much more expensive. Therapeutic studies also require much longer patient follow-up and monitoring for safety and overall survival (in the case of cancer therapies), which also significantly increase the costs.

***Dr. Herrmann:*** *So, as a rule of thumb, how many-fold more expensive is a therapeutic trial than a diagnostic trial?*

**Mr. Buono:** From my personal experience and observation in the market, I would say it is at least 10 times more expensive to develop a therapeutic drug than a diagnostic one.

***Dr. Herrmann:*** *Good to know. The majority of the theranostic experience currently comes from Europe; however, the focus of future revenues lies clearly in the United States. Does this create a challenge for companies?*

**Mr. Buono:** The general rule of thumb for any drug or any device in medicine is that at least half of the global market is represented by the United States. I actually see more of a challenge in how nuclear medicine therapies are approached as either in- or outpatient procedures as the larger challenge for companies seeking adequate reimbursement rates. For example, PRRT is generally considered an outpatient treatment in the United States, which enables an easier separation of certain hospital costs from the cost of the drug. However, in Europe, we are mostly seeing this procedure as an inpatient administration, where drug and overall hospitalization costs are reflected on the hospital budget. Being reimbursed on the basis of drug cost versus the full cost of an inpatient procedure is completely different. This is a very key element that drives the difference in reimbursement between the United States and Europe, and I believe this represents an opportunity for Europe to reduce costs for such procedures, which will further support the development of nuclear medicine therapies in Europe.

***Dr. Herrmann:*** *You left the CEO role at AAA after the acquisition by Novartis in January 2018. When you are now looking at AAA, what are your hopes for this company for the next 5–10 y?*

**Mr. Buono:** I hope and believe that AAA will remain a leader in the nuclear medicine industry, driving overall growth in the sector. I have seen only an acceleration in growth since the company was acquired. I am very optimistic about the future of AAA.

***Dr. Herrmann:*** *What do you think as a private citizen (not as an AAA representative) about further increasing vertical integration—for example, not only producing and distributing the therapeutics but also opening and running theranostic centers, especially in areas without expertise or interest in theranostics? Based on the German experience (40 theranostic centers for 80 million people) the United States would need around 160. I believe that 70–80 will be built by interested institutions, but there might be a shortage of centers. Does it make sense for a company to tackle the challenge of the last mile by setting up theranostic centers to treat patients?*

**Mr. Buono:** My personal opinion is that this concept creates a conflict of interest. During our early days at AAA, we never wanted to run PET centers because we saw it as competition with our own customers. This was a line we never crossed.

***Dr. Herrmann:*** *How do you see the future of PRRT?*

**Mr. Buono:** I would actually start by asserting that part of the future is in the way in which we refer to this therapy. One of the fantastic things that Novartis did when they acquired the company was to start using the term "radioligand therapy," instead of only PRRT. As an industry, I think we should use this term for the future, because it represents a much wider field than PRRT alone. It opens up the possibility of different types of ligands, not just peptides.

The future is really bright for this type of therapy, if we can overcome a few big challenges. One is the inpatient administration of this therapy in Europe. I think the United States model proves that patients do not have to be treated in special rooms and stay overnight. I believe there is little risk involved in letting the patient go home at the end of the day and having them back with their families, as long as they avoid intimate contact. This is an important step impacting perception of the overall cost, as well as implying greater complication and danger of nuclear medicine procedures. We need to stop demonizing nuclear medicine.

Another challenge is the reimbursement of nuclear medicine diagnostics. In Europe, nuclear medicine imaging procedures are reimbursed in almost every market—but not the drugs used in these procedures. This is a limitation for the entry of new and innovative imaging drugs. In the United States, there is a 3-y grace period for the separate reimbursement of imaging drugs, but then it is much more complicated. Diagnostic drugs deserve our attention, as they are an important part of the theranostic approach. If we solve these points I am convinced the future will be more than bright for the entire industry.

***Dr. Herrmann:*** *Talking about the future: do you think that the concept of theranostics is just a 1-hit wonder, or do you believe in theranostics as a platform technology with different targets, different ligands, and different isotopes?*

**Mr. Buono:** I strongly believe that it is a platform technology. We were motivated by the goal of developing such a platform. I always said that I believe the impact of theranostics, especially in oncology, would be comparable to that of immunotherapy.

***Dr. Herrmann:*** *A recent JNM supplement focused on the future of nuclear medicine. I would like to pick your brain on a couple of topics, such as how theranostics should be included in training of physicians. Should nuclear medicine with theranostics be an independent specialty or rather be integrated within internal medicine, radiation oncology, or radiology?*

**Mr. Buono:** This has been THE topic of the last 15 y within nuclear medicine. It is a very difficult question to answer. We see that cancer is increasingly being treated by multidisciplinary teams. Each case involves multiple specialties, and, ideally, this also includes nuclear medicine, although it is not always the case. As more institutions take such a multidisciplinary approach, I feel the issue should become less relevant in the future. If an oncologist could administer nuclear medicine drugs, it would accelerate the success of nuclear medicine and enormously expand the field. Of course, this requires proper training.

***Dr. Herrmann:*** *From a development point of view, what do you prefer? Self-development or some kind of licensing?*

**Mr. Buono:** I think that both self-development and licensing are important for success. One idea is to find potential candidates in the libraries of pharma companies. Many clinical candidates don't make it to approval because of toxicity. Maybe they are good targeting agents, but they are too toxic. These candidates, for example,

could be excellent candidates to be labeled with radionuclides. We normally inject only micrograms or even less of a nuclear medicine drug with little to no pharmacologic effect, because we are relying on the radioisotope to be the active ingredient. It was always my dream to convince companies to do such a review and start new developments. I'm sure that from there we might find something very interesting.

***Dr. Herrmann:*** *When do you think is the right time point to reach out to big pharma? It makes sense to do it early on to access the libraries. On the other hand, there are certain things you probably did as a small independent company that couldn't be done within a big company. So when is the right time point to attract big pharma?*

**Mr. Buono:** Historically, it has been difficult to motivate big pharma to enter the nuclear medicine space. But we see the environment is changing, and more money is flowing into nuclear medicine. Biotech companies have more resources to look at things. The predicted success of Lutathera has certainly driven the attention of companies into nuclear medicine.

***Dr. Herrmann:*** *Finally, I want to ask you about your personal future. Are you going to initiate a next-generation AAA, or will your focus be more on your philanthropic activities?*

**Mr. Buono:** I have already started some nonprofit activities, and I also founded a single-family office, Elysia Capital. We invest in relatively early-stage projects across different fields: biotech innovation, social impact, well-being, education, art, and culture. Out of a total of 24 investments made to date, only 7 are in biotech or medicine. I also sit on the board of a public company, Abeona, which is a U.S.-based biotech focused on cell and gene therapy in rare diseases. I am the chair of Planet Smart City, which is a company that originated in Italy and is building smart cities and affordable housing communities with a current focus on Brazil and India. I also recently accepted the position of chair of a business foundation to foster technology transfer in Italy. I look at this as part of my personal contribution to my community since I returned to live in Italy.

***Dr. Herrmann:*** *I missed 1 thing: I heard a rumor that there is also a big sailboat involved?*

**Mr. Buono:** Yes. I had a 20-m carbon catamaran built. I hope to launch soon, and in June next year we're going to start off on a round-the-world trip with the family. I have 2 kids, who are now 8 and almost 6 y old, who will join the trip aboard this fantastic boat.

***Dr. Herrmann:*** *Stefano, thank you very much for your time. It was a pleasure to talk to you and our readers will appreciate your insight very much.*