I'm grateful for the invitation to MedConference and I'm honored, and happy, to be here with you. I'm expected to talk about research and treatment for trisomy 21, however the purpose of my talk is not to give a formal review on these themes, but a personal perspective arising from things that have happened in my work and in my life in very recent years.

Down syndrome (DS) is the most frequent constitutional form of intellectual disability in humans. It was only in 1866 that a British medical doctor, John Langdon Down, published his work that recognized that the typical symptoms of the syndrome allow the definition of a distinct pathological entity. His description is based on the hierarchical racial classification system accepted during his time, and due to the resemblance of facial features of individuals with DS to those of individuals of Mongolian origin, he named the syndrome "Mongolism". It should be noted that in this system Caucasians are superior to all other races and Mongolians are at the bottom of the ladder. For approximately a whole century there was no substantial progress in the understanding of DS.

The main symptoms include intellectual disability (ID), cardiovascular defects and craniofacial dysmorphisms. Despite ID being measured by a test of symbolic logic skills, it is common for children with DS to arouse a climate of affective intensity greater than the norm. A recent study asked people with DS, ages 12 and older, about their self-perception, finding that the overwhelming majority of people with DS indicated that they are happy with their lives, liked who they are, liked how they look and expressed love for their families, indicating they live happy and fulfilling lives [Skotko et al. 2011].

In 1958 the young Parisian medical doctor Jérôme Lejeune discovered that DS children have one extra copy of chromosome 21 in their cells [Lejeune et al. 1959]. This historical observation marks the beginning of medical genetics: for the first time in the history of medicine, definite symptoms were linked to a specific alteration of the genetic material. It is remarkable that this observation came not from theorists of genetics, but from a physician who routinely visited children with DS for five years before his discovery, and he became convinced that it was not an infectious disease, which was believed at the time.

In addition, the social consequences were, if possible, even greater. Up to that point, most children with DS were kept segregated, in institutions or in their homes. Their parents were suspected to be alcoholics, syphilitic or even immoral, and there was the possibility that one would walk away when running into them with their child. It would be difficult for us to imagine what these families had to cope with. The discovery that there was a definite organic cause for the syndrome gave a dignity to the condition, and it was a liberation for the families because the cause of the disease had a name, and it was a chromosome, a solid piece of organic matter, and not a strange behavior. The derogatory term "mongolism" was abandoned.

This new feeling brought by this discovery is best represented by Bruno, a trisomic young man that at the end of the funeral Mass for Lejeune in Notre Dame in 1994 took the microphone and said to the crowd in the church, "Thank you, my professor, for all that you have done for my father and my mother. Thanks to you, I am proud to be me. Your death has healed me" [Lejeune-Gaymard 2012]. It was then learned that he was one of the first children from whose karyotype analysis Lejeune made his discovery of trisomy 21 35 years before.
Lejeune was born on June 13, 1926 at Montrouge, near Paris, and he graduated in medicine in 1951. In the following year he married the Danish Birthe Bringsted, and they had five children. In Paris, he always stayed home for breakfast, lunch and dinner, and when around the world, he wrote a letter to his wife each night.

Trisomy 21 is due to an unpredictable error of cell division while preparing ovocytes or spermatozoa.

It has a natural frequency constant all around the world: 1 in 400 conceptions and 1 in 700 births. It is the most frequent genetic condition in humans, and it appears as a standard error of human cell division.

In a minority of cases one of the two parents, although healthy, brings a translocation involving chromosome 21 that increases the risk of having a child with trisomy 21.

The only known non-genetic factor increasing the risk of DS is maternal age.

In rare cases, the zygote, the fertilized ovocyte, i.e. the one-cell embryo, is normal but can present a mutation during its early development leading to trisomy 21. In these cases, some cells are normal and some cells are trisomic, and it is assumed that the syndrome will appear if the mutated cells are the majority.

In 1969, when this fact was poorly understood, Lejeune stated: Intermingled with all the preceding cases is the cumbersome problem of mosaicism. Every human being is a mosaic due to some mitotic malsegregation in some part of the body; the dividing line between normal and pathologic is a matter of percentage: if 50% of abnormal karyotype is considered as deleterious, what about 40%, 20% and 5%, and what about topographical distribution? [Lejeune 1970].

I was really struck when I stepped onto a scientific article published only in 2005 reporting that in all normal human brains 2% of neurons have trisomy 21! [Rehen et al. 2005] In a certain sense, we are all trisomic 21, and it's really only a matter of percentage. If you consider that we also have an additional 2% of neurons with monosomy or tetrasomy 21, and that the study is focused on only one of the 23 pairs of human chromosomes, I'm wondering how many really normal neurons each of us has, this perhaps explains some non-linear behavior sometimes I find in myself (and, quite frankly, in others too). This relevant fact underlines the difficulty in labeling one's heritage as normal or not.

This extraordinary picture of a Madonna with Child from Andrea Mantegna, a great artist of the 1400s, is believed to depict a mother with a child with DS. You can note the enlargement of the thyroid making the neck swollen, likely due to hypothyroidism in the woman used as a model, and the typical aspect of a child with DS.

It is impressive how the child gazes toward his mother. He shows upslanting eyelids, a flattened nose root, and an opened mouth, as well as a typical larger than normal space between the first and second toes. However, it is important to note that, first, no one of these aspects is sufficient to make a diagnosis of DS, which can be present in their absence or absent in their presence, and, second, that these and other symptoms are not relevant from a medical point of view. The actual problems are a language production deficiency and cognitive impairment, which is present to some degree of severity in all affected individuals and which involves symbolic thought, whereas affectivity and social skills are conserved.

This historical premise is necessary to understand the point where we stand in the research and treatment of trisomy 21, and most of all, why.

From 1959 to 1969, Lejeune was one of the most famous and listened to scientists in the world. In 1962 he received the Kennedy prize from the hands of the president of the United States, John Kennedy; in 1965 he was the first in France to be appointed to the Chair of Fundamental Genetics; he was awarded the "William Allan" prize, the most important honor in Genetics, in 1969.
This event was a landmark in the life of Lejeune. In front of hundreds of colleagues brought together to recognize his work, he gave a memorable speech [Lejeune 1970], transcribed in the "American Journal of Human Genetics", affirming that geneticists were betraying the aim of medicine, which was not prenatal diagnosis oriented to selective abortion, but rather healing patients. However, at an international level pressure was mounting toward the legalization of abortion, starting from the cases with a recognizable alteration of development, and fetuses with trisomy 21 became the first candidates for abortion. This fact explains the subsequent ostracism that Prof. Lejeune had to suffer from the scientific community: he was never awarded the Nobel prize, he had no more pay raises, and he had difficulties in obtaining funds for his research. Writing on the walls at the Faculty appeared claiming: "Dr. Lejeune and his little monsters must die" [Lejeune-Gaymard 2012]. But, most importantly for this discussion, this explains why active research for a therapy of trisomy 21 was almost stopped. I have found that, from 1992 to 2012, there have been about 4,500 articles published in the biomedical literature about prenatal diagnosis compared to less than 10% of this number directed toward a basic therapy for this condition.

This effort has undoubtedly been successful because we now have the first test for diagnosing trisomies in the mother's blood, without the risk of villocentesis and amniocentesis. When I saw this article one year ago, I thought: now this test will be proposed to all pregnant women, not only those at risk. Timely, an article just appeared proposes exactly this. However, also this test is subjected to a small percentage of errors that are not totally avoidable by definition in any diagnostic method. It should be noted that in Europe 90% of women with a prenatal diagnosis positive for trisomy undergo abortion, and that the rate of it is lower where the society supports children with disabilities and in particular with DS.

Lejeune stated: People say, “The price of genetic diseases is high. If these individuals could be eliminated early on, the savings would be enormous!” It cannot be denied that the price of these diseases is high—in suffering for the individual and in burdens for society. Not to mention what parents suffer! But we can assign a value to that price: It is precisely what a society must pay to remain fully human [Lejeune "21 Thoughts"].

Lejeune also recounted that still in France at the end of the 1700s, those sick with rabies were suffocated between two mattresses. A few years later a child was born, Louis Pasteur, who accepted the challenge to fight rabies and discovered a cure.

There is a second reason for the difficulties with DS research: it is a hard and challenging work. While in the most studied genetic diseases, such as muscular dystrophy or cystic fibrosis, there is only one gene causing the symptoms, in DS we have an entire additional chromosome, bearing at least 234 different protein genes, and it is not clear which of them cause the symptoms. However, the order that we can see in this complex scenario is that the neurological alterations observed in DS are constant and well distinguishable from those observed in other genetic conditions with intellectual disability. A really original suggestion came from Lejeune when he considered the trisomic cells as "drug addicted", intoxicated by the excess of gene products, like enzymes and other proteins that are formed in the cells due to the presence of the additional chromosome. A molecule of DNA, a chromosome, is like a pizza pan: if you have an excess of pans you will produce an excess of pizza. If we knew which mechanisms are slowed by the excess material produced we could devise a more specific therapy.

You will not find this photo of Lejeune around because it is a scanned original printed photo owned by Prof. Maria Zannotti, a former Professor of Genetics at the University of Bologna. She was a fellow of Prof. Lejeune in Paris for several months in '67 and '69. This was the morning meeting, when Lejeune revised the karyotypes assembled by his fellows. His laboratory was a center of diffusion of medical genetics all over the world. Prof. Zannotti is sitting to the left of Prof. Lejeune, and she still remembers his kindness, his passion for science, his attention to everyone in the lab. Thirty years later, I was entering the University of Bologna enrolled as a researcher, following eight years of fellowships after my degree in medicine. I was working in Experimental
Hematology, and she proposed to me to work on DS because I was also in charge of teaching Genetics. I readily replied, "I wouldn't even dream of it." I knew that DS was the first genetic condition to have been discovered, so I was afraid that it was an overcrowded field of research. She insisted, pointing by chance to a gene on the chromosome 21 map, "Why should we not study this?" To prove that she was in error, I searched the biomedical literature databases for articles about that gene, imagining that there were hundreds. I could not believe that there were only two articles about that gene. In a few years, we published seven reports about that gene family, and it was a colleague of mine working in my group, Lorenza Vitale, who described a new large gene on chromosome 21 which had been not identified in the first virtually complete catalogue of chromosome 21 genes published two years before [Vitale et al. 2002]. However, at the end of 2000 years we were demotivated and tired. We had no funding, no new ideas and no conviction that we could ever bring a contribution toward a cure of DS.

We were actually closing this line of research. On March 11, 2011, it just so happened that my friend Dr. Mark Basik was in Europe and he asked me for a ride from the Bologna Airport. In the car, we talked about our work, and Mark said, "You must go to Paris, in two weeks there will be an important congress about DS." You must now know that I come from a wonderful small Italian city, Fermo, whose name means "still". When in Bologna to study medicine, as a first year medical student I attended lessons of Histology and Biology in the same department where I also prepared my thesis for the degree, had my PhD and post-doctoral activity, became enrolled as a researcher and then as an associate professor. I am still locking my bicycle each day to the same pole I chained it 30 years ago. Really, I can't be considered an excellent testimonial for the international fellowship programs. This is also the reason why my English, as you are hearing, is slightly different from yours. So I readily replied "I wouldn't even dream of it". However, I remained impressed by Mark’s enthusiasm. He said that his friend Dr. Ombretta Salvucci would be there, having known the family of Lejeune. I felt that it could be a good occasion to relaunch our research, however I continued to see lots of reasons that made it impossible for me to go to Paris... They were all proven to be only excuses when challenged, so in the end I took that plane. This journey radically changed my attitude toward DS research. I listened to many top scientists firmly convinced that DS could be cured. I figured out how a new bioinformatic software we had just published could be used to solve some problems about the localized gene expression on human chromosome 21. But most of all, thanks to Ombretta, I was given the gift to know Lejeune’s history and his extraordinary family better. I discovered a man of exceptional intelligence, a great physician and a researcher with ideas many years ahead of his time. I learned about persecutions he suffered for having stated that medicine was abandoning patients with DS, favoring prenatal diagnosis. I was particularly struck by the fact that a beatification process was happening, with many graces attributed to his intercession. I saw the Lejeune’s books, and I could not believe he studied general informatics. He had foreseen the development of bioinformatics because DNA sequence is pure information. He used to say: *In the beginning is the message, and the message is in life, and the message is life. And if the message is a human message, then the life is a human life.*

But the genial geneticist and biochemist was the same pediatrician who visited thousands of children with intellectual disability, encouraging their families, highlighting the enrichment in humanity experienced by so many families because of the presence of a person with DS and not only the problems. Lejeune was the person who dedicated all of his life and so much love to these children, who all called him "my professor", and at the same time he would correct the biochemical errors which hamper the full expression of their human abilities and he used to say: *Hate the disease, love the patient: that is the practice of medicine.*

The wife of Prof. Lejeune, Madame Birthe, asked me about my work and I stuttered something about human chromosome 21. She simply said to me, "You must see patients." Back in Bologna, I continued to think about this invitation, but it was very challenging for me. I had seen a patient for the last time during my licensing exam for the admission to the professional exercise of Medicine in 1991; after that I only saw test tubes and computer monitors in the lab, with many academic duties and lots of lessons to give. In addition, I was not excited at the idea of starting from
zero in a clinical environment. So I thought: this will never happen, and I never called my colleagues. Some months later, Professor Guido Cocchi, who I did not know, phoned me for a faculty task, and I was aware he was following more than 130 children with DS... so I was not able to refuse this perfect opportunity to go back to the clinic. I talked to him about my history and for more than one year I have been regularly attending his Neonatology Day Hospital one day a week. Please imagine the first time I was following a visit, at the end of the line of his older and younger assistants. I appeared to be an old medical student still studying, amazed at everything and asking about it all, when I was identified by two very surprised doctors as the professor who examined them in Genetics eight years earlier and was now learning from them... I think this is a gift that I have been given in the true spirit of the university and of research in which we are all students forever and we can learn from each other every day.

This activity, which is so unusual for me, has proven to be central for the reprise of our research on DS, for at least four reasons.

1. The first reason is that you learn what the real problems of the patients are only by seeing them and getting to know them. We need to recover the attitude of simply watching what's going on in reality. Following my first days in the clinic, my strongest impression was that the cognitive deficit was less serious than I had learned from medical literature. And, although the speech problems are underlined in scientific articles, only seeing these children and listening to their parents allowed me to appreciate that their self-perception is of a high level and that we might erroneously judge that they are not understanding, while they are understanding very well but are unable to express their thinking. In particular, I observed this on two occasions. The child with DS of a friend of mine, when he was three years old, got sad and angry when a music CD with children's songs had been playing. He clearly gave signs that the CD should be removed, then he precisely located and indicated CDs by the band "Queen" and by Bruce Springsteen. Despite the so-called "cognitive deficit", his musical tastes were years ahead of his peers! At the end of a talk where I spoke about this, a parent said to me, "It's incredible, because my three year old child only wants to listen to songs by Bruce Springsteen!" So this could also be a new research line about the preference for rock in DS...

On a second occasion, we were passing from one room to another in the Day Hospital, the corridor filled with children and parents. Suddenly, a nine year old girl with DS, surprising even her parents, got off her seat, her hands clasped, shouting, "Doctor, I am in a hurryy!!!" Everyone in the hall laughed out loud, with someone asking. "So, you are in a hurry, where do you want to go?" She answered, "Home!"; "Oh, to do what?" "To play!" I was struck by her, I thought, "This child has a perception of the value of her time that I have never seen in a child with the regular number of 46 chromosomes." She was giving the doctors this message: don't think that I am at your disposal, I have my life, I have to do many things and you're wasting my time. These and other facts have taught me that the most superior states of the human consciousness, the capacity of perceiving the beauty, the self-consciousness of the I, are well preserved. Lejeune affirmed that the most superior capacity of humans with respect to animals is the capacity to admire. So, the logical and symbolic tests used to measure the intelligence quotient do not account for the whole reality of the person, and they regard activities that may be compromised at a mechanical level for neurological damage that could be rescued.

2. The second advantage of clinical observation comes from cases behaving unexpectedly. These cases often offer the key to uncover an elusive mechanism. In this regard, we believe that it is critical to accurately investigate the very few persons with DS and nearly normal Intelligence Quotient. One day I was called back to the Day Hospital to specifically see a two year old child coming from another city for medical advice. He had no clear morphological sign of DS, and he was looking around as if he were thinking, what am I doing here? I was impressed by the information that his family pediatrician refused to give him exemption from the cost of care based
on the fact that he judged him to be cognitively normal. However, he had a full free trisomy 21 in all of more than 20 metaphases studied. In similar cases, one of the possible explanations is that the excess chromosome is not complete, and by molecular cytogenetics we could discover which segment is lacking, finding that it contains genes critical for the symptoms of DS. We also believe that accurate review of all cases of partial trisomy 21 will contribute to the understanding of the genetic mechanisms of the disease.

3. A third aspect of clinical research is the possibility to explore the wide range of presentation of symptoms and to relate them to specific genetic alterations. While the in vitro models tend to provide homogeneity, clinical reality provides diversity, and it would be very useful to begin the study with subgroups of patients located at the extremes of the variability, in terms of number and severity of symptoms. The extreme situations may again shed light on critical mechanisms.

4. Last, but surely not least. Seeing patients offers strong human motivation to struggle to help real sick people and not abstract nosographic entities. It also helps to devise approaches that are most likely to find applications in medicine and not sophisticated manipulations possible in cells or animals but not in humans. From this point of view, the most relevant change that seeing patients gave to my research was that before, I was searching for a cure for DS, and now I am searching for a cure that may improve the lives of Davide, Andrea, Chiara, Gabriele, Anna and so on... It's a different thing. In addition, it has been an unforeseen gift to know and to admire the parents of the children. After an unavoidable period of shock following the diagnosis, if the parents accept the child, in the course of time the most diverse people come to the same conclusion: he (or she) has changed our family; our family became stronger and filled with love; we could not imagine our life without him/her; he/she led us to rediscover the essentials of life.

Due to the fact that ID is the most constant symptom in DS and the one most affecting daily life of persons with DS, for the purpose of this talk we refer to a "therapy for DS" as a cure able to improve the cognitive state of persons with DS.

We can do interventions aimed to relieve some specific symptoms or complications of DS, but, to date, no therapy is recognized and recommended by guidelines as being effective in improving the cognitive abilities of persons with DS.

The search for a causal, radical therapy has been directed to a few main lines of investigation that I will quickly list [reviewed in Costa et al. 2013, Strippoli et al. 2013].

1. Chromosome inactivation

A breakthrough in research about human chromosome 21 has been the demonstration, published this August, that this chromosome can be inactivated in vitro by transferring the gene which is able to switch off one of the two X chromosomes in female cells to one of the three chromosomes 21 present in trisomy 21 cells.

Interestingly, Lejeune appears to have been the first to have gotten this suggestion from nature, as he writes in 1988: The most obvious therapy of a trisomic condition would be to silence the extra chromosome (...). Indeed nature is that shrewd and inactivation of supernumerary X chromosomes is a very efficient trick. Unfortunately the basic mechanism is still unknown. It presently seems that many problems must be resolved before this discovery can even be applied. In particular, an effective method to transfer the method in living humans must be found. In any case, this new line of research could have unexpected consequences on the field of DS research.

2. Neurogenesis stimulation
It is an established fact that a defect of cell proliferation, and in particular of neuron proliferation, is present in DS. Following the finding that antidepressants may stimulate neurogenesis in the hippocampus, a target organ in DS, the use of fluoxetine or lithium has been proposed. The open issue in this case is the feasibility of the administration of powerful mood stabilizers, with potentially serious side effects, to a pediatric population based on studies conducted on mice.

3. Neurotransmission modulation

Alterations of neurotransmission and of functions of selected brain regions in DS are specific of this condition to a certain extent but, to date, interventions with drugs active on the central nervous system have obtained limited or controversial results. Lejeune's hypothesis was to "detoxify" neurons where the implied pathways would be clarified, restoring normal function to the obstructed, backed up synapses. For this, he insisted on the need of a more detailed knowledge of the biochemistry of the involved processes and of their relationship to chromosome 21.

4. Vitamins and antioxidants

Recent reviews in the field fail to find evidence in favor of administration of different vitamins, antioxidants, or their combination as treatments for DS. Further investigation is needed to identify more aimed dosages or combinations that could be effective, in possibly some, if not all, subgroups.

Lejeune proposed a path toward a cure based on the integration of multiple types of information, aimed at finding the actual mechanisms implied in the generation of the symptoms. We have extracted several relevant methodological principles from his articles.

1. Have a positive hypothesis about the existence of a solution

Now in the case of Trisomy 21 I am not at all going to say the cure is just around the corner. I don't know, but we know enough to consider that on theoretical grounds the idea that nothing could be done because it had an extra chromosome is not warranted. On the contrary, because it has an excess of normal material they probably have some prediction of normal things but at too great an extent and if we could just block this prediction they would come back slowly to normal [Lejeune 1992]. These and other similar statements of Lejeune have been critical for us to recover a positive attitude toward the possibility that trisomy 21 might be cured. Maintaining a position of doubt about success in research leads to quitting, while continuing to be in an attitude of question leads to active research. "A real search always implies a positive answer as an ultimate hypothesis otherwise one would not search" [Giussani 1997].

2. Pursue systematic and open study of biological mechanisms

A typical problem faced by the investigation of a complex system is the ability to identify components that are critical for a certain process. We need to explore the object in all directions to find critical checkpoints.

It is barely known that Prof. Lejeune was the first to, to our knowledge, envision system biology application to the understanding of trisomy 21. He conceived a surprising mechanical machinery mimicking several tens of chemical compound interactions known at the time.

The powerful and popular image of the search for a single musician playing out of time within a great orchestra has also been used by Lejeune to simply express his belief that human reason has the ability to identify tiny disturbances in a complex but ordered context.
3. Try to interpret any finding in the context of the chromosome physical map

From this "geographical" point of view, accurate analysis and continuous monitoring of any report about partial trisomy 21 remains important because even single cases may allow for the exclusion of a main role for a chromosome 21 gene if it is not present in three copies in subjects showing a typical DS phenotype.

Remarkably, this could to be the case for \textit{DYRK1A}, one of the chromosome 21 genes most studied as a gene relevant for the phenotype. In October 2012, a Turkish child was reported as having a typical DS phenotype, partial trisomy 21 and absence of one excess copy of \textit{DYRK1A}. This fact should be taken into serious account by rediscussing current models that give an established a critical role of \textit{DYRK1A}, which is inhibited by green tea extract, for causing DS.

4. You must see patients

When in 1988 the beginning of a more systematic characterization of the human genome appeared not to be impossible, Lejeune immediately highlighted the need that the forthcoming effort of DNA sequencing predicted as fundamental for understanding DS pathogenesis should remain tightly linked to the patient: \textit{the tedious and laborious comparison of the clinical data and of the DNA deciphering is, currently, the starting point of any pathogenic scheme}.

Keeping in mind the main methodological points that we have derived from the knowledge of the scientific thought of Lejeune, we have come to the conclusion that it could be worthwhile to launch an innovative research project on DS aimed at systematically integrating clinical, biochemical, genetic and bioinformatic data obtained in humans in order to identify reliable therapeutic targets for this form of trisomy [Strippoli et al. 2013]. The primary outcome of the proposed approach is to gain new knowledge about the genotype-phenotype relationship in DS, focusing on ID, in order to reduce the list of hundreds of genes located on the human chromosome 21 to a very small number of elements.

We therefore propose a project aimed at producing both experimentally and by meta-analysis state-of-the-art maps and databases related to clinical/phenotype, cytogenetics, exome, transcriptome, methylome, molecular biology, metabolome and mutations data. The prudent pace we are faced with seems to us a realistic alternative to giving up as well as to giving false hopes.

A fundamental part of our study, able to help connect its various sections, will be the reprise and the study of scientific articles by Jérôme Lejeune because, apart from their contribution to a solid methodological approach as we have pointed out above, you can find in them specific hypotheses that in many cases appear not to have yet been verified or falsified, such as the seven metabolic pathways he discusses in his 1988 review.

Let me go toward the conclusion adding another less known aspect of the extraordinary personality of Lejeune. Most of you know that on May 13, 1981 John Paul II survived an assassination attempt. But most likely some of you would not know that the last person that the Pope received at lunch before going to the square was Dr. Lejeune with his wife. When Lejeune was informed about the attempt against the Pope, he himself was hospitalized on the same day, with painful gallstones, and he underwent surgery and was discharged on the same day of John Paul II [Lejeune-Gaymard 2012]. In 1997, during World Youth Day in France, Pope John Paul II insisted that he could travel to the small town of Châlo-Saint-Mars, where he prayed at the grave of Lejeune, who he called "my brother", who had died at the age of 67 from lung cancer on April 3, 1994 in Paris. The beatification process of Jérôme Lejeune is now transferred to Rome.

I would conclude with two sentences. The first is from Bruno, the trisomic man mentioned in our Introduction: \textit{I met him many times, he discovered trisomy with me! He used my karyotype, number 380 is mine. The scientific research must be continued. I am glad to know that advances are...}
continuing. Professor Lejeune was a friend of those who were handicapped. Professor Lejeune is close to me [Association Les Amis du Professeur Jérôme Lejeune].

The second is from Lejeune. While seriously sick, he was worried for his patients. I was the doctor who was supposed to cure them and, as I leave, I feel I am abandoning them.

We will beat this disease. It's unconceivable that we will not. It will take much less intellectual effort than sending a man to the Moon [Lejeune-Gaymard 2012]. Landing men on the Moon is still inspiring those today who are trying something that seems impossible. It is known that the Apollo Project involved the work of more than 400,000 persons with a budget which was up to 5% of the US total federal budget. Although there has recently been an unexpected reprise of interest for DS research, we are often working with limited resources. We are also starting systematic fund raising initiatives, such as that which can be accessed from our web site "Apollo 11", whose success will be critical for the feasibility of the project.

Finally, Lejeune was convinced that everything is interrelated. If I find out how to cure trisomy 21, than that would clear the way for curing all the other diseases that have a genetic origin. The patients are waiting for me; I have to find it.

I would suggest the reading of the wonderful book by Clara Lejeune, "Life is a blessing", about her father.

And I would give very special thanks to the few persons in Bologna that have remained with me following the relaunch of our research on trisomy 21: Lorenza Vitale, Maria Chiara Pelleri, Allison Piovesan and Maria Caracausi.

When I was so kindly invited by Dr. Elvira Parravicini to come to United States to tell this story, I immediately thought, "I wouldn't even dream of it". You know the conclusion. Thank you for your attention.

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**Essential References**

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[http://apollo11.isto.unibo.it](http://apollo11.isto.unibo.it)

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Lejeune J. 21 Thoughts

Lejeune J. Articles by Prof. Lejeune


