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Review

Origin of personalized medicine in pioneering, passionate, genomic research

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ABSTRACT

Personalized medicine, one of the main promises of the Human Genome Project (HGP) that began three decades ago, is now a new therapeutic paradigm. With its arrival the era of developing drugs to suit all patients, yet often having to withdraw a promising new one because a minority of patients was at risk, even though it had proved valuable for the majority was consigned to history as were trial-and-error strategies being the predominant means of tailoring therapy. But how did it originate and the earliest examples emerge? Is it true that the first personalized diagnostic test was the companion test for Herceptin®? This account of a remarkable journey from genomic and translational research to therapeutic and diagnostic innovations, describes how sequencing the human growth hormone (*hGH*) locus provided proof of principle for HGP-inspired personalized medicine. Sequencing this locus and the resultant biomanufacture of HGH and the development of a test capable of detecting which patients would benefit from its administration helped silence the skeptics who questioned the validity of such an approach. The associated companion diagnostic was created four years before the invention of the HercepTest® (registered as the first companion diagnostics ever developed). By cultivating genomic research with passion and pursuing its applications, we and many others contributed to the emergence of a new diagnostics industry, the discovery of better actionable gene-targets and to a revitalized pharmaceutical industry capable of developing safer and more effective therapies. In combination, these developments are beginning to fulfill the promise of the HGP, offering each patient the opportunity to adopt the right treatment at the correct dosage in an opportune manner.

1. Fishing a gene for my genetic journey: the *chorionic somatomammotropin* gene from human placenta

Molecular cloning, invented in the early years of the decade of 1970, arose an international fever and race to clone human genes. For the rest of that memorable decade, and throughout at least the first half of the next one, many genes were "fished." And their study exploded a golden era of human molecular genetics and unleashed a new biotechnology revolution. The first ones, or so-called *low-hanging fruits*, were those whose messenger ribonucleic acids or mRNAs were abundant in the tissues in which they were quite active or from tissues that were easily accessible. Perhaps the best example in molecular genetics was the *β-globin* gene since peripheral blood cells are both full of its mRNA and easy to get a hold of, while in biotechnology they were human growth hormone and insulin.

At the beginning of the decade of 1980, I was a graduate student in the Biochemistry Department of the University of Texas Health Science Center at Houston, in its then called MD Anderson Hospital and Cancer Center. Being in one of the largest medical centers in the world, the fever also got me, and I, too, wanted to clone a gene.

As early as the summer of 1978, I was extracting mRNA from the human placenta and, through its translation in a cell-free system (*in vitro*), I noticed that one of its most abundant mRNA species was that of the then called human placental lactogen (later baptized as human chorionic somatomammotropin or HCS). I frequently visited the library to learn, from Nature or Science magazines mainly, which new gene was reportedly being cloned. One day, I read that Peter Seeburg, who had just moved from the University of California at San Francisco to the recently launched, first biotech company of the world, Genentech, Inc., had just cloned a fragment of the complementary DNA (cDNA) to the mRNA of this placental hormone thanks to an ingenious trick. He had converted all placental mRNA species to cDNA, and, as a bulk, treated them with restriction enzymes. Next, he separated the restricted products by gel electrophoresis and cut out, cloned and characterized the most abundant, discrete cDNA band. This band, of around 500 base pairs (bp), turned out to be the central region of the *hCS* cDNA. Since he knew that HCS and human growth hormone (HGH) were highly similar proteins, he moved quickly to use his partial *hCS* cDNA clone as a probe

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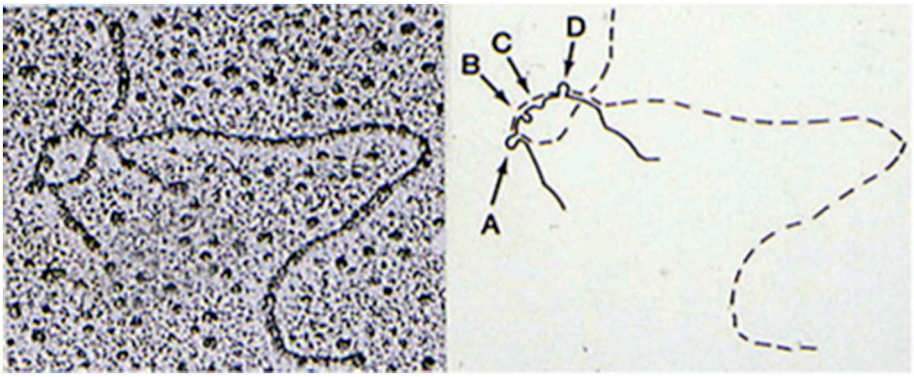

Fig. 1. Anatomy of the genes harbored in the *hGH* locus. By hybridizing a strand of the gene with its complementary DNA and searching for the resulting heteroduplexes in the electron microscope, we discovered four introns (A through D) splitting the gene into five exons.

or hook to pull out, from a cDNA library made of a hypophyseal adenoma cDNA, the cDNA of the *hGH* gene, putting it aside to complete the cloning of the full-length *hCS* cDNA.

Peter kindly shared with me his probe and I used it to screen the human placental cDNA library I had just constructed. I pulled several cDNA clones very easily, including one harboring the full-length *hCS* cDNA. This way I was one step away from finally cloning the *hCS* gene myself. Using my clone, Vincent Kidd in our laboratory screened a human genomic library and pooled several positive gene clones that were characterized by making preliminary restriction maps of each one. I quickly identified among them the one matching restriction mapping features of my *hCS* cDNA. I incubated both, the gene and full-length cDNA, under conditions that favored heteroduplex formations between them (suggested by Donald Robberson, an expert in electron microscopy). When Donald and I examined them in the electron microscope, we noticed four small "bubbles" (see Fig. 1). We interpreted them as corresponding to an equal number of sequences in the gene which were absent in the cDNA, which means we had just discovered the four small introns that interrupt the message hidden in this split gene [1].

2. Pioneering genomics research: *hGH* locus, a chapter of our hereditary encyclopedia

The multiple genes pulled from the human genomic library screening with my *hCS* cDNA proved to be a cluster of genes which I was able to assemble into a pentagenic *hGH* locus and together with Mary Harper we revealed its position in bands q22–24 of the long arm of chromosome 17, being the first time ever that a so-called single copy gene was assigned its chromosomal position in the human karyotype. Besides the emblematic gene named *hGH-N*, which is the one responsible for the production of HGH in the somatotrophs of the hypophysis, this locus of our genome happened to contain an additional *GH*-type gene, *hGH-V*, which in the placenta produces a variant of the hypophyseal hormone that is postulated to replace it exclusively during the gestation period of pregnant women. It also includes two placental genes whose cDNAs I had pulled out during the screening of my placental cDNA library and discovered that, surprisingly, their mRNAs code for an identical mature HCS. Finally, there was this third *hCS* gene whose corresponding cDNA I could not identify among the clones I had fished out during the screening of my placental cDNA library, nor by trying at least two other cDNA characterization methods [2].

To explain the mystery of this last *hCS* gene, I turned again to Peter Seeburg to share with him my findings and he arranged with my doctoral adviser, Grady F. Saunders, for me to spend time in his laboratory at Genentech to sequence entirely and for the first time this mysterious gene, which turned out to harbor a mutation at the beginning of its second intron known to render the genes presenting it inactive or pseudogenes. We baptized it as *CSH-Like* or simply *CSH-L*.

Before returning from Genentech to my laboratory in Houston, Peter and his colleague, Elson Chen, invited me to contribute this gene sequence to an unusually ambitious and weird project, which involved sequencing the entire *hGH* locus, genes and their intergenic and flanking regions and of the locus itself, which in total we estimated that would encompass over 60,000 nucleotides (see Fig. 2).

I gladly accepted their invitation and, back at my bench in Saunders's laboratory, I continued to curate the crude sequences I had just brought from Seeburg's laboratory. Reading the genes was relatively easy; however, assembling the intergenic pieces separating them was a difficult task, since they harbored half a hundred repetitive elements of the *Alu*-family. Nevertheless, besides the sequence of *CSH-L*, I helped too by having solved the pentagenic structure in which this and the other four genes of the locus were assembled. When we completed curing the locus sequences (see Fig. 3) about five years later (it took us so many years since it was a side project for all of us, especially for me since by then I was already in Mexico starting my own laboratory), we had decoded an equivalent to a chapter of an enormous encyclopedia which we now know it consists of almost twenty-five thousand chapters, which as a whole conceals the secrets of our species: *our genome*.

While this project was going on, I graduated, went to France to do a postdoc, and returned to Mexico to start my own laboratory. In 1989, the job was finally done, and the manuscript was submitted and readily accepted for publication in *Genomics* [3], the leading journal of the nascent discipline with this same name: genomics. Our achievement was soon noticed by the scientific community and mentioned in the magazine *Science* as a world record for the largest piece of human genomic DNA ever sequenced, becoming the first evidence that, if technology could be greatly improved, it would be feasible to launch a project that would involve sequencing the entire human genome, which was later known as the *Human Genome Project* or simply HGP.

But what did our quixotic achievement teach us about the use of sequencing the whole genome which took place almost fifteen years later? Well, that when you have the genomic sequence of your genetic research model, you have uniquely valuable information that you could dig into or do its "mining" to design experiments to solve the ultimate questions about the origin, composition, functioning, and consequences of dysfunctions of our hereditary instructions; even more, and with a bit of creativity and the proper challenges, to exploit it for deriving inventions!

In our case, wishing to prove in my laboratory the usefulness of having sequenced our tiny piece (0.0016%) of the human genome, we launched ambitious projects that led to the achievement of a myriad of inventions and discoveries that we never imagined would have such an impact later on in medicine and biotechnology [4]. Here I have chosen two inventions of my laboratory that illustrate the value of genomic information in advancing medicine and biotech.

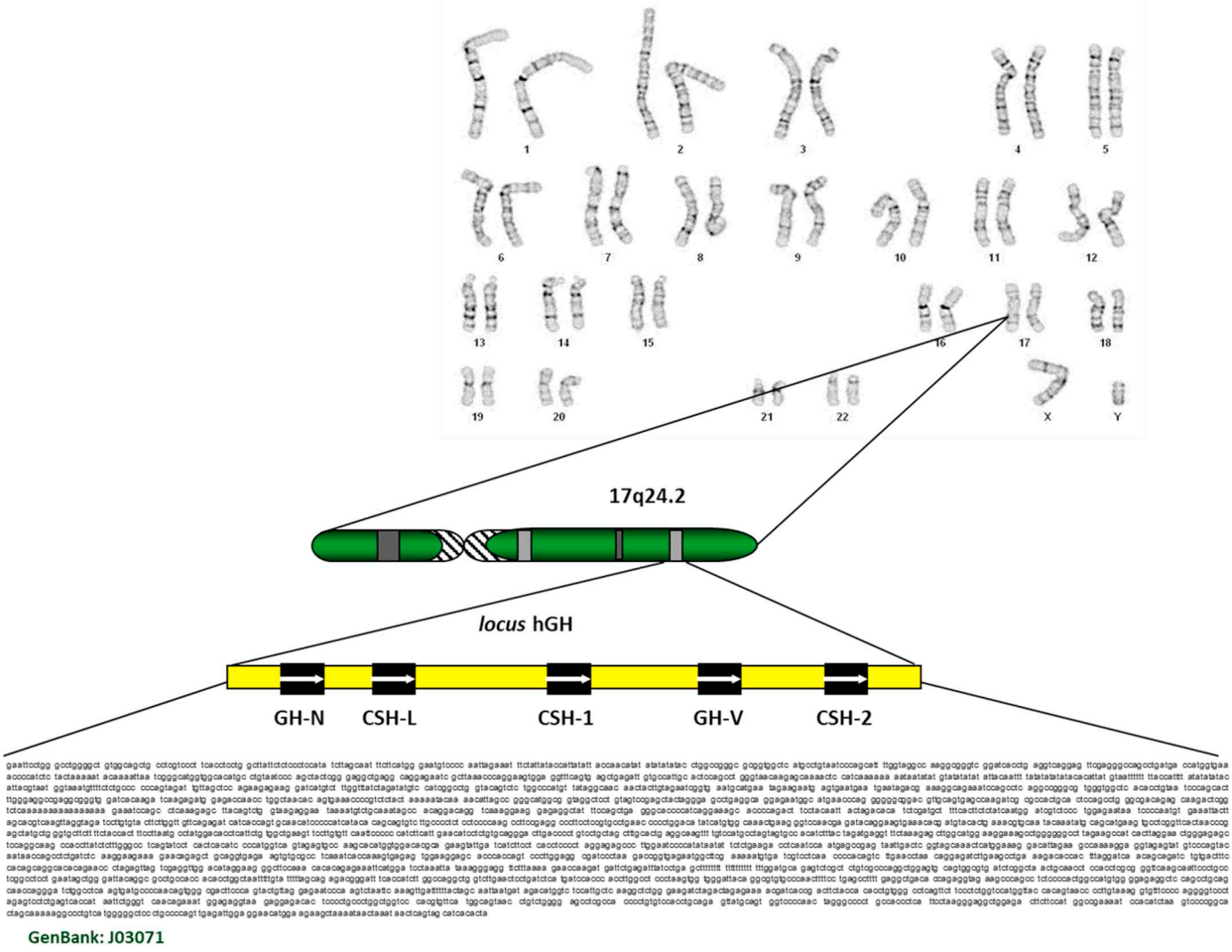

Fig. 2. Sequencing the *hGH* locus of our human genome. The locus was isolated as a pair of large clones fished out from a genomic library with the cDNA probe. To facilitate its sequencing, it was spread into a few dozen smaller clones. The assembled and curated sequence was deposited in the GenBank sequence database with accession number J03071.

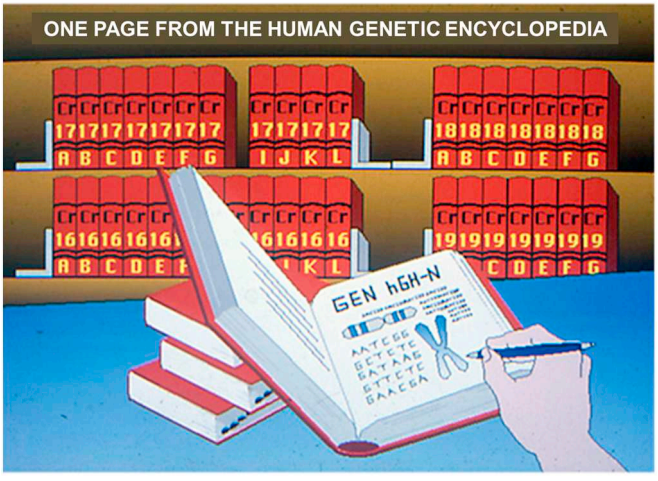

Fig. 3. The *hGH* locus chapter of the human hereditary encyclopedia. This over sixty-six thousand string of nucleotides is equal to a chapter of the monumental encyclopedia that is our genome.

3. Initial mining of the *hGH* locus sequence for advancing biomedical research

How is it that, being encoded by genes showing more than 90% similarity in their flanking regions (and even more in their coding ones), being so close to each other in the genome, and having been derived from a common ancestor not so long ago, they display such marked differences in their pattern of expression both spatial (different tissues) and temporal (at different times of our lives)-specific?

Not only is *hGH-N* set apart by its hypophysis-specific expression, but also by the fact that its expression is shut down in pregnant women to allow the placental members of the family to control the maternal metabolism to ensure the survival of the human fetus. Likewise, not only is the expression of the so-called placental genes restricted almost exclusive to the placenta, but it is also synchronized with the development of the placenta itself.

So, where do the secrets for regulation of their tissue-specificity and temporarily-governed gene expression reside? When in addition to the five coding sequences of the genes in the *hGH* locus, we consider their introns and the space separating them (intergenic regions) and add up the flanking sequences we adventured to read too, it turns out that this gene family encompasses approximately 66,000 nucleotides (66 kb). It was precisely by dissecting these gene-flanking DNA zones that we were

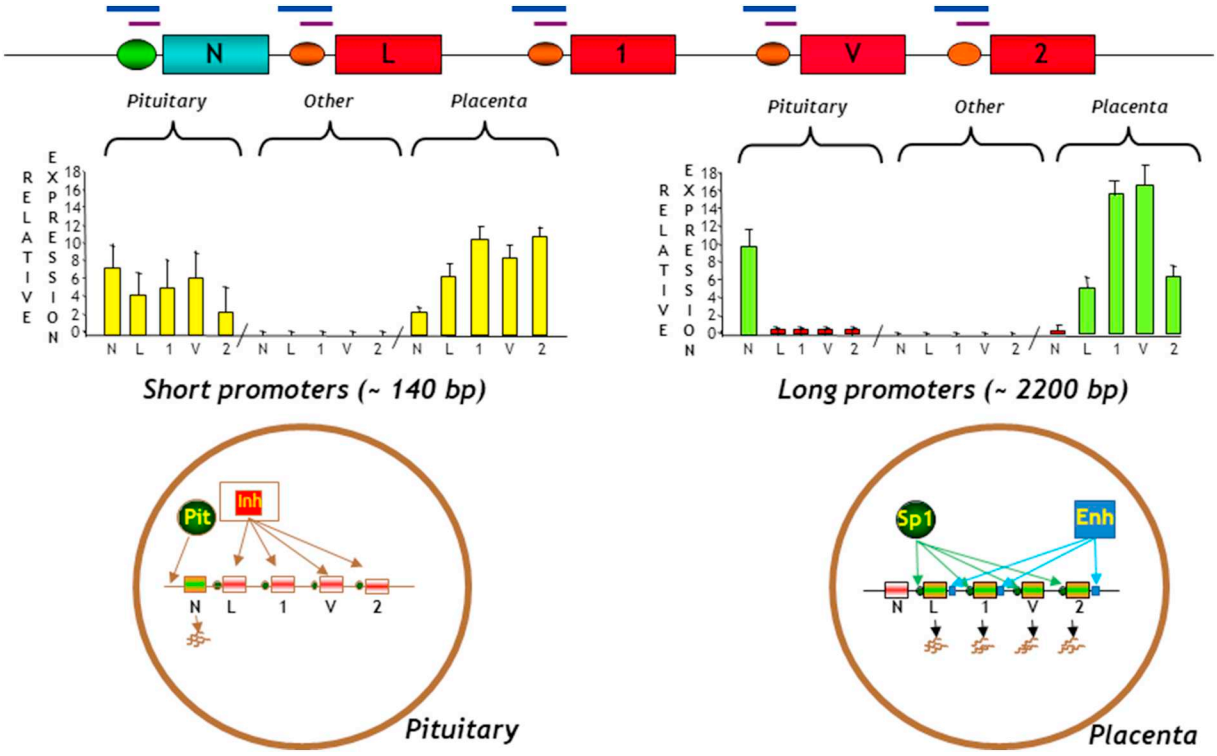

Fig. 4. Differential gene expression control in the *hGH* locus. Despite their high structural resemblance, close genomic proximity and, to some extent, overlapping functionalities, only the *hGH-N* gene is active in the pituitary gland while the rest are active in the placenta. The secret to this spatial expression difference lays in the genes' promoters acting as switches and responding to diverse gene activating and repressing factors.

able to discover the main mechanisms regulating its differential tissue-specific expression, as illustrated in Fig. 4. One such mechanism is exemplified by Pit-1 (pituitary transcription factor 1, also known as growth hormone factor-1) acting on the promoter of *hGH-N* to induce the transcription of this gene in the pituitary but unable to do so on the rest of the genes (*GH-V* and *CSHs*) as a result of their promoters containing a region of 0.3 kb, referred to as element P, to which certain placental proteins bind, interfering with Pit-1's binding. Another mechanism is through the enhancer, which is an expression control element that potentiates transcription of the adjacent gene(s). In the case of the *hGH* locus, this happens to be located right after the *hCSH* genes, thus explaining the amazingly high production of CSH by the human placenta at the end of pregnancy, with quantities surpassing one gram per day! Therefore, to control the spatial (different tissues) and temporal (only during pregnancy) expression of a gene family, the human genome devotes ten times more DNA than that needed for specifying the hormones codified in this family (see Fig. 4).

Seeking to further exploit this discovery in order to contribute to the advance of the emerging field of viral vectors for gene therapy, we took advantage of the tissue specificity of the gene's promoter to control the replication mechanism of adenoviral vectors so as to develop re-engineered viruses that were capable of selectively replicating within cultured hypophyseal tumor cells that were then burst by induction of cell lysis, while leaving any other type of normal cells intact. When we were exploring to move this discovery to the preclinical stage, we started a similar project for the development of a similar treatment but for cervical cancer, that was more rapidly and successfully tested in an animal model. This incursion in the field of gene therapy of my laboratory led by my former student Augusto Rojas and by then my fellow departmental colleague, finally led to a collaborative project with colleagues from Baylor College of Medicine in Houston that allowed us to implement the first clinical trial for cancer gene therapy ever carried out in Latin America. In it, we administered also an adenoviral vector but carrying a gene from another virus that contributes the unique biochemical capability of phosphorylating a nucleotide analog that when incorporated in the recipient cell halts its DNA replication (precisely for this reason this approach is referred as suicidal gene therapy) [5].

4. Industrial exploitation of our chapter of the human genomic encyclopedia: rHGH

By the time the publication describing our seminal work on genomics came out, I was struggling in Mexico to consolidate my laboratory in a kind of avant-garde scientific desert. My mission, I was convinced, was to introduce and cultivate Human Molecular Biology, which back then was the most promising scientific discipline in medicine. Even though I was madly working on consolidating my laboratory, I could not resist the temptation of bragging our world record. But, to whom? Not only was there no other molecular biologist in a 500-mile radius (the approximate distance from Monterrey to Houston) with whom I could discuss the relevance of our achievement, but most of the few professionals around me were skeptical clinicians from our nearby University Hospital. And since they were more concerned with saving lives, they invariably reproached me when I presumed my world record repeatedly questioning me: *what possible use, in the daily battle they were fighting at the hospital, could such genomic information that I had in my hands have?*

My new environment was indeed unique. On one side I was struggling to stay in the world-class academia and thus was working like crazy to establish the new research and graduate programs of my young laboratory so that my existence and that of the new discipline I brought with me would be noticed by the administration. This battle, I was fighting from my modest bunker in a corner of an abandoned section of the Department of Biochemistry at the University of Nuevo Leon Medical School in Monterrey, Mexico. On the other side and just across the street were all these rocket-science questioners in the clinical departments of the said hospital, where I had managed to make many new

friends. Soon, some of them challenged me to prove that our achievement had at least some practical use in the clinic. I gladly and arrogantly accepted their challenge.

The opportunity to prove to them that our pioneer genomic research indeed had some useful application in medicine came the day I least expected, but luckily soon enough. One day, our Dean called upon me to his office to inform me he had invited the state governor to visit the hospital and he wanted me to be present during the visit. He also informed me that he was planning to invite a few other colleagues from among the most restless and vivacious researchers in the faculty that he respected and truly wanted to help their careers. Moreover, he also mentioned that he was expecting for all of us to take this unique opportunity to impress the governor with our sophisticated research projects. He had planned that, if we could make a positive impression, the governor could contribute funds to the hospital and part of them would be used to support our work.

My colleagues, when exposing their plans to the governor, ended up making a request for large and expensive pieces of equipment (the larger and more expensive the better!); I guess with the rationale that if their work was in the forefront of science, it demanded such sophisticated tools. I instead, and to the surprise of the governor, simply asked him to instruct the State Attorney to grant me prompt access to the pituitary gland of cadavers of people who died from traumatic accidents and that are typically sitting at the morgue while their relatives show up to claim them. The next day I received a call from the State Attorney office with a positive reply to my unusual request. Soon, I had the glands from some twenty cadavers, collected shortly after an exceptional fast-track autopsy of the dead bodies just after their arrival at the forensic laboratory in our hospital, immediately put in dry ice, and quickly transported to the ultralow freezer of my laboratory. There were long nights due to grant deadlines when this messenger from the forensic laboratory appeared in my office to hand me a new gland. I felt like Victor Frankenstein and pictured the messenger as Igor, Frankenstein's assistant. '

Why did I want the hypophysis of cadavers, you ask? Well, to emulate what Peter Seeburg had so ingeniously done to clone the *hGH* cDNA mentioned above which, after a law settlement with UCSF for several millions of dollars, was licensed to Genentech to produce recombinant (r) HGH. Good enough, the approach worked perfectly and from the cloned, restriction enzyme-digested, total cDNA from the cadaveric hypophysial mRNA (see Fig. 5), we easily isolated our own version of the *hGH* cDNA [6].

But what was this gland's genetic instruction useful for? Well, our body uses it to command the synthesis of HGH, which is why I thought of using it to reprogram a microbial biotechnological host to produce rHGH. This with the aim of eventually offering a national, technological alternative to the few ones from abroad rendering commercial rHGH (including the one my friend Peter had developed for Genentech). This biotech blockbuster was badly needed by our pediatricians and endocrinologists to treat patients suffering from the partial absence of this hormone, so they could offer them the chance to achieve normal height and thus escape from the otherwise inevitable destiny of suffering from severe dwarfism.

We tried out our idea with the new yeast, *Pichia pastoris,* which was quickly dominating the list of favorite biotechnological host for genetic engineering applications. And it worked beautifully for the first time! We got transformed yeast to produce and secrete, into the culture media, rHGH, which we proved to be identical to that present in the human hypophysis and even more: it was abundantly secreted into the fermented yeast media in its biologically active form [7].

Our new method to produce rHGH was so novel and innovative that we convinced the USPTO and another patenting office in Europe and Japan, in addition to the one in Mexico, to grant us the patent, protecting our invention (see Fig. 6). With it in our hands and after having successfully demonstrated it worked at pilot plant scale, we were able to raise the interest of the first Mexican biotech firm to license our technology to produce rHGH in Mexico. This way I had proven to my fellow clinicians that genomics can lead to the availability of a - I was hoping - more affordable rHGH.

We followed our success of using the cDNA transformation of yeast for producing rHGH to reprogram yeasts using the cDNAs of the remaining genes of the *hGH* locus so that they could produce the rest of the hormones encoded by these genes. We did the same with cDNAs cloned from a dozen plus animal GHs and even prolactins and CSHs. These genetic engineering experiments resulted in the world's largest collection of recombinant somatolactogens, a name collectively given to all these different types of body growth and metabolic regulators.

5. Medical exploitation of our genomic data: *diagnosing HGH absence*

Even though I felt I had succeeded in proving to my fellow clinicians, who were skeptical at first, that genomic information had, in fact, some practical value by attempting to help them with an

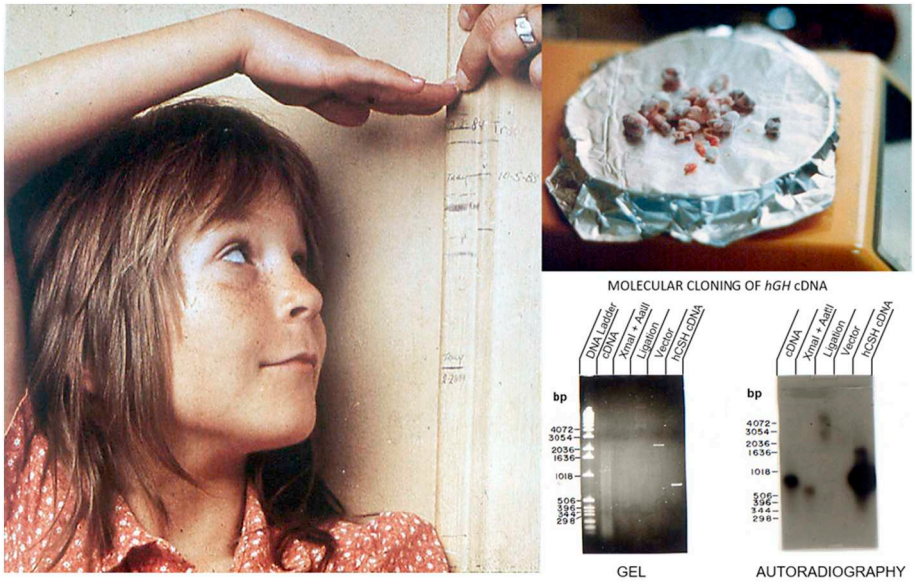

Fig. 5. Cloning the *hGH* gene's complementary DNA. Having opportune access to the pituitary glands from cadavers allowed us to clone the genetic instruction our body uses to synthesize HGH. Its deficiency by the dysfunctioning of the corresponding gene causes dwarfism, which can be reverted by replacement therapy with the biosynthetic or recombinant (r) hormone as Tracy profited of it back in the early 1980s.

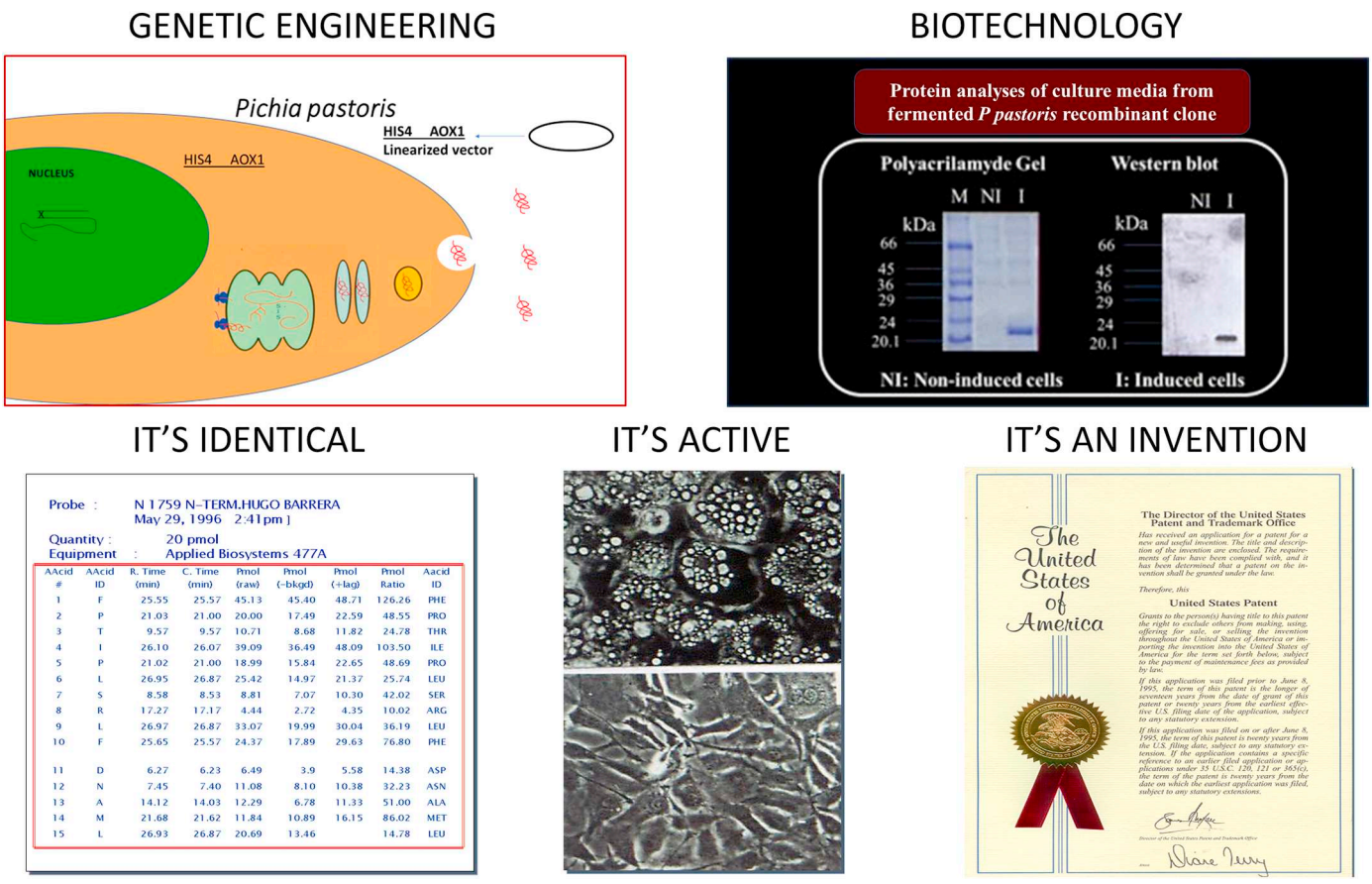

Fig. 6. First ever production of rHGH in yeast. Cloned *hGH* cDNA was introduced in the genome of yeast whose fermentation resulted in the secretion, into the medium, of biologically active biosynthetic or rHGH that was identical to that naturally produced by our body – invention that gained an international patent.

alternative biotechnology-produced hormone, some of them were not completely convinced, yet. Thus, they gave me a second challenge: *to help them predict which children would respond to replacement therapy with rHGH and to distinguish them from those few that unexplained till then wouldn't.* The only piece of information we had in face of this challenge was that those children unable to respond had no reduced amounts of the hormone, but rather lacked it totally and when treated with the biotechnologically produced version, their immune system rejects it, since it recognizes it as a foreign protein (or antigen, in this case) and makes antibodies to neutralize it. With my over optimism of the value of the genomic information I treasured in the *hGH* locus, I once again accepted this new challenge by them of not only explaining this enigma but also contributing a way to genetically identify these exceptional children and to alert the pediatricians over the useless of prescribing them rHGH.

Fortunately, my laboratory in Monterrey, Mexico, was by then (early 1990´s) some kind of sanctuary of science, attracting the best youth to the glamorous human molecular biology I had introduced to my country upon my arrival from the best laboratories in the world that were advancing this new discipline. Also, to my fortune, I had just returned from Chile, where I lectured at a Human Genome workshop that exposed me to the newly-invented polymerase chain reaction (PCR). In addition, some of my best students were being seduced by bioinformatics and were practicing it with their modest, personal computers by reprogramming, at night, powerful computers at the International Center for Genetic Engineering and Biotechnology Center of Trieste, Italy. So, not only did I have all these new wonderful tools at hand, but also, of course, the unique advantage of being among a handful of individuals in the world in possession of the complete sequence of the *hGH* genomic locus. Thus, I assigned to one of my students, as his BSc thesis subject, to come up with a PCR test to differentiate patients that had the *hGH* gene intact from those lacking it. This quest would be the laboratory explanation for the former kind of patients' positive response to the hormone replacement therapy, and for the latter type of patients' rejection of it. We soon had the scheme of the diagnostic assay that we proved right using cloned versions of the genes that we mixed to reconstitute an artificial *hGH* genomic locus. Next, I turned to my most harsh critics in the pediatric clinics and requested them to provide me with blind samples, *i.e.* samples whose data I did not have and thus didn't know their respondent/non-respondent condition, from ten of their young patients clinically diagnosed with severe growth retardation. Sure enough, during the first application of our newly designed genetic test, we spotted one patient that lacked the *hGH* gene and predicted that they would be a non-responder [8]; my fellow clinicians later confirmed this was indeed the case (see Fig. 7).

6. Did you say a test that predicts the outcome of treatment with rHGH? You have invented the first *companion diagnostics*, you dummy![1]

It was by wanting to prove to skeptical clinicians that pioneer genomic research could have practical benefits, that the first ever

[1] A FDA report refers as the first achievement in personalized medicine the approval on September of 1998 of Herceptin for the treatment of HER2 positive metastatic breast cancers and on the same day of its companion test HerceptTest to DAKO Corp (www.fda.gov/downloads/scienceresearch/specialtopics/personalizedmedicine/ucm372421.pdf). However, our use of the sequence of the *hGH* locus to develop a genetic test usable to predict response to rHGH, published as a BSc thesis in 1994 and as a scientific paper in 1997 is, to the best of our knowledge, the first such achievement and thus the detonator of the era of the so-called personalized medicine.

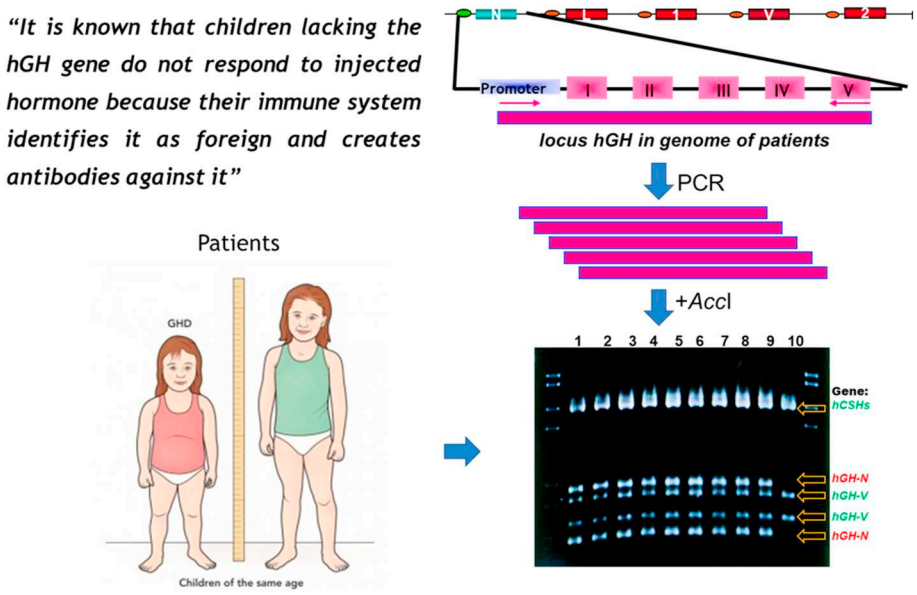

Fig. 7. A genetic test to identify HGH-deficient patients that would not respond to replacement therapy from those that would. Bioinformatic analyses of the sequences of the five genes of the *hGH* locus allowed us to design a simple polymerase chain reaction with just one pair of consensus primers to amplify them. Digestion of the mixture of amplicons with *Acc*1 restriction enzyme should render four digestion products as a ladder of bands: the first and last bands are digestion products of the gene responsible, in the hypophysis, for the synthesis of HGH (*hGH-N*), while the second and third bands are evidence of the presence of the placental gene counterpart (*hGH-V*). Moreover, these last conveniently act as an internal control to verify the test worked fine (they should always be present).

Table 1
Timeline and history of personalized medicine.

Genome and personalized medicine: milestones
1. More than two and a half millennia ago Hippocrates stated: "it's far more important to know what person the disease has than what disease the person has"
2. In 1956, "favism," the genetic basis for the selective toxicity of fava beans, was discovered to be due to a deficiency in the metabolic enzyme G6PD
3. In 1985, Renato Dulbecco realized that, in order to advance cancer research, it was necessary to sequence the human genome
4. In 1988, our laboratory joined colleagues from Genentech, Inc, in sequencing the entire *hGH* locus (a world record), making evident the feasibility of sequencing the Human Genome
5. In 1990, the Human Genome Project (HGP) was launched and the first draft was published in 2001, while its final version in 2003
6. Since the early 1990s, individualized treatments tailored to the genome of each patient were envisioned but rarely realized
7. In 1994, our laboratory designed a diagnostic test for the prediction of the success of rHGH replacement therapy, being the earliest registry of a Companion Molecular Diagnostics (CMDx) test ever invented
8. In 1998 when FDA approved Herceptin (anti-EGFR mAb for $EGFR^+$ breast tumors) and HerceptTest (to detect such tumors) it became the first "official" CMDx invented
9. Since then, a growing list of diagnostic packages/personalized medicine therapies has received, from the FDA, labels recognizing and recommending them

designed companion diagnostic test was invented. The test was just perfect, since, in addition to only needing a single pair of PCR consensus primers for simultaneously amplifying each of the five genes in the *hGH* locus, it sufficed to follow the PCR with a digestion with a single restriction enzyme to reveal if the gene coding for HGH (*hGH-N*) was present or not in the patient's genome. Moreover, and to add to its elegance, it also identified, among the amplified products, the one responsible for the placental counterpart of this hormone (*hGH-V*), and its presence in the gel used to resolve the digested products acted as an internal control to demonstrate that the test had technically worked. This feature was quite convenient, since, as Carl Sagan used to say: "absence of evidence is not necessarily evidence of absence," and this "internal control gene" detection feature of our test, made life simpler in diagnostic laboratories with only modest molecular biology infrastructure.

This genomic information-based diagnostic test not only served as the companion diagnostic for this inaugural product of modern biotechnology, rHGH, but also as a versatile tool to investigate gene alterations in the rest of the genes of the *hGH* locus, soon to be proven when explaining the extremely rare condition of total absence of CSH in an otherwise uneventful pregnancy having found in such cases that gene deletions of the *CSH* genes are their common underlying causes [9].

So, catapulted by our research passion, surrounded by talented youth, trying to revert a scientific gap and to cope with a health disparity, and on top of that, provoked by our pride to prove science is the most powerful tool to advance medicine, we had made world-pioneer discoveries and inventions that contributed to the dawn of at least two monumental historical enterprises of the life sciences of the last half of a century: the *Human Genome Project* and *Personalized Medicine* (see Table 1).

While the Human Genome Project has revolutionized biomedical research and detonated waves of new biotech start-ups, Personal or Precision Medicine has become a global aim of governments to cope with the unsustainable rise of expenditure in health and to drastically reduce the estimated approximately 10% of the unnecessary hospitalizations due to adverse effects because of errors in drug prescriptions and in their dosing.

We, as others like us in the world daring to dream of doing world-class science in their adverse scenarios, are kept encouraged by our string of achievements, as modest as they might be. With them, and if we persevere, we ended up touching the lives of many. First, of youth venturing themselves in science. Second, of responsible and even heroic health professionals wishing to offer more relief to the disease burden of their patients. And third, of brave men and women wanting to use science to create businesses and better jobs to help revert the limitations of the local scientific capabilities and the disparities of our afflicted contemporaries. If we persist and see the day come when our dreams are fulfilled, we must feel extremely lucky and proud of having paid back part of our debt to society, for the enormous privilege of having been trained in academic centers of excellence to join the army of men and women advancing medicine with the torch of science.

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