



Gayle De Maria

Girindus Leadership in Oligonucleotides Symposium G.L.O.S.

GAYLE DE MARIA
Chimica Oggi / Chemistry Today
gayle@teknoscienze.com

Girindus, a service provider to the pharmaceutical industry and a leading manufacturer of therapeutics oligonucleotides, held the first Girindus Leadership in Oligonucleotides Symposium (G.L.O.S.) on March 31st - April 1st in Cincinnati, Ohio, USA. This inaugural event showcased high level technical talks from leaders in the oligonucleotide field and provided valuable and timely information for scientists.

Chimica Oggi/ Chemistry Today had the honour to participate in this event as the only representative of the scientific press and to listen to all the speeches and furthermore interview the President and Chief Operating Officer of Girindus America Inc, Mark Laskovics, and Tadeusz Wyrzykiewicz, director of the oligonucleotide group.

For those who are not familiar with Girindus it can be interesting to read a few lines on the history of this company as presented by Mark Laskovics during our interview held on the second day of the event.

Girindus AG, a family-owned German company, was founded in 1975 as an independent trading company whose aim was mainly to buy chemicals from suppliers and sell them to clients. Realizing that trading was not so viable with the advent of the internet, the company decided to have its own chemical plants; these plants were bought from Astramedica – Degussa's pharmaceutical company. In 1986 Girindus USA was established and the company had its IPO on the Frankfurt stock exchange in 2000. In 2001 Girindus acquired the Aventis Pilot Plant in Cincinnati and completed building a new Biotech and QC Laboratory in Kuensebeck, Germany. The company moved in this way from a trading company and started its contract manufacturing business. The original plan was to have an early development presence in the USA doing the preclinical through Phase 2a work in Cincinnati then transferring the projects to the large plant in Germany



for Phase 2b, 3 and commercial manufacturing. "There are some structural reasons why that did not work out", stated Laskovics. "In my experience only about 5% of the small molecule projects in phase 1 and 2a advance to phase 2b so there were few opportunities to transfer to the larger plant. In addition when our clients, which are small to intermediate sized pharmaceutical companies, did an evaluation about where to perform their Phase 2b scale-up they tended to think locally". "They wanted to place the project in their home economic region; US clients tended to scale-up in NAFTA and European clients tended to scale-up in the EU". "When Girindus purchased the Cincinnati facility and established its cGMP manufacturing group, the company grew rapidly thanks to the value-added relationship created with clients and the solid-phase oligonucleotide synthesis

What are the main challenges of Girindus?

From the history of this site we were a preclinical - phase 2a operation for big pharma so what do we know from that?

- we have worked on a wide range of chemical projects
- we had high level of expertise in organic chemistry
- we knew how to move things through the development of phases
- we understand the urgency of getting a compound made so you can quickly move through phase 1-2a studies to find out if you are even going to have a drug
- and most of the time when you work in that area speed and timeliness are the most important things because people don't want to waste a lot of money especially on the small molecule side when there is only a small 5% chance to go to phase 2B. They want to find out as early as possible if the molecule is going to late development phase or if it is going to die.



Mark Laskovics

And so we have that culture of being very responsive and we also have some services that we can bring to the table, analytical services and analytical method development, which is necessary when you start industrialization, and radiochemistry services. In that culture we started the oligonucleotide business and again we are responsive and technically competent and that is the team we built. And now what is happening is that oligonucleotides are going into the late development phases, 2B, validation, phase 3, so the next thing to do is to turn the culture of our company into a commercial culture. And we are investing heavily in the quality area; we have just appointed the new Vice President of Quality, Steven Broadbent. We have to have a commercial mind set. Our vision is to be the preferred commercial supplier of oligos and to build that here in Cincinnati. And also to bring to the table our small molecules expertise...From this perspective there are a lot of other chemistries that can be supported in the oligonucleotide area like delivery systems. We have areas where we can provide our small molecule expertise to better support our oligo clients.

business started in 2002", pointed out Laskovics. The State of Ohio moreover provided Girindus a 1.2M\$ *Third-Frontier Grant* to build the first oligonucleotide scale-up facility. In 2005 Solvay's chemical division, which was looking into developing a high value business, acquired the majority in Girindus. Solvay had, in fact, peptide synthesis experience and was interested in Girindus' oligonucleotide expertise in order to have a "tides" portfolio to offer to its clients. "Thanks to this acquisition we gained the technical expertise we needed, for example engineering consulting for construction projects, and financial stability", affirmed Laskovics. During the symposium Girindus unveiled its 5.2M\$ expansion wing whose construction was made possible thanks to Solvay's financial support. "The Symposium is a celebration of the new plant and a way to show off our investments and have the opportunity to meet potential clients and exchange views", Laskovics told us.

Let's leave for a while what was discussed during the interview with Girindus representatives, to understand why this symposium on oligonucleotides was so important also from a scientific point of view. To do this it is necessary to give an overview on what oligonucleotides are and what are their applications.

Firstly, for the uninitiated, an oligonucleotide, in the strictest sense, is a short piece of nucleic acid less than 50 nucleotides in length. In the past 20 years, the meaning has broadened to include all chemically synthesized nucleic acids, regardless of the length. The landmark paper published by Watson and Crick in 1953 which described DNA's double helix structure determined the birth of molecular biology. It was only natural that chemists would soon have an interest in trying to synthetically prepare these molecules. In the late 1950's professor H. Gobind Khorana of the University of Chicago introduced two concepts that made possible the convenient synthesis of oligonucleotides – the protocol was then called the phosphodiester method of oligonucleotide synthesis: 1) the on-off protection scheme necessary for sequential oligonucleotide synthesis; 2) the first use of a stable phosphorylated nucleoside that coupled onto the desired nucleoside when activated. Khorana's most lasting contribution, however, was in the areas of nucleoside protecting group. The solution Khorana offered for 5' hydroxyl protection – the dimethoxytrityl (DMT) protecting group – is ubiquitous in oligonucleotide chemistry. Professor Khorana influenced many with his work like Marvin Caruthers who developed the phosphoramidite method and Robert Letsinger who developed the solid phase synthesis and the phosphate-triester chemistry. Letsinger collaborated with Kelvin Ogilvie who succeeded in synthesizing the RNA molecule that initiates protein synthesis in living cells (1). It is not the aim of this article to enter into biological and chemical details of how oligonucleotides are synthesized but we wanted to give a quick overview on the history of oligonucleotides synthesis and a basic background to our readers so that they can understand why it was a great honour for us to participate in this symposium where Caruthers and Ogilvie were keynote speakers.

What are the main technologies used in Girindus?

We pride ourselves for being experts in solid phase oligonucleotide synthesis able to tackle any synthetic problem posed by contemporary oligonucleotide-based medicines. Higher generations of the oligonucleotide drugs usually carry diverse array of exotic nucleoside, heterocyclic base and backbone modifications. We are prepared to work on any of developed chemistries that were disclosed or not disclosed to general public. Thanks to our oligonucleotide expertise we are confident that we can deliver projects, regardless of their complexity in a timely and satisfactory manner. Our elongation chemistry is based on solid phase technology. It is not a secret that other CMOs are using this technique too. The basic concept of this technology is deceptively simple. Multiple adjustments introduced to the process during the last several years and overlapping intellectual property issues are adding the complexity of oligonucleotide manufacturing. This area requires a lot of very specific knowledge in order to manoeuvre projects to their successful delivery. Current demands of oligonucleotide market do not require metric ton quantities of APIs and can be easily delivered by solid phase technology. During early stages of drug development usually time is a crucial factor and you do not have luxury of devoting a lot of efforts to process development and optimization. From that perspective Solid Phase Technology is definitely superior. However, once the later stages of drug development are reached then price of API and underdeveloped aspects of large scale manufacturing come to the surface triggering interest in alternative scale up strategies. Therefore, Girindus had and still has an internal R and D program focused on alternative oligomerization techniques including solution phase chemistry. The main philosophy behind scaling-up on solid phase is development of the uniform scale up platform allowing for easy scale-up once process parameters, developed at smaller scale, are optimized. This concept was the main driving force behind design of the manufacturing trains at Girindus. All of our trains allow for seamless transfer of developed process parameters.



Tad Wyrzykiewicz

Oligonucleotides can be used as therapeutic agents or tools to study gene function. Over the past 2 decades the antisense oligonucleotide technology has emerged as a valid approach to selectively modulate gene expression. Its development as therapeutic agent has led the Food and Drug Administration approval for the commercialization of the first antisense oligonucleotide, Vitravene – for cytomegalovirus retinitis – Isis Pharmaceuticals Inc/ Ciba Vision, and then for Macugen NDA – for the age related macular disease – Eyetech Pharmaceuticals, Inc. By adhering to a strict set of specific rules, ongoing *in vitro* studies using antisense oligonucleotides permit the characterization of new targets and new potential therapeutic compounds. The number of *in vitro* experiments has increased continuously, and this has led to numerous therapeutic trials, a few of which now appear, in a preliminary stage, to be positive. However, the optimal use of antisense oligonucleotides in the treatment of disease requires the resolution of problems relating to effective design, enhanced biological activity, and efficient target delivery.



Kelvin Ogilvie and Marvin Caruthers

These issues were addressed during the Symposium organized by Girindus who managed to put together a group of very high level quality speakers who represent the past and the future of oligonucleotide science. The past is certainly represented by the two keynote speakers, Marvin Caruthers and Kelvin Ogilvie who respectively talked about some milestones in the oligonucleotide history and a focus on cellular uptake of phosphonoacetate DNA (Caruthers) and the first 40 years of oligonucleotide synthesis (Ogilvie). The future is definitely represented by all the companies and universities who showed their advancement in this field. But let's enter into details of the lectures and get to know more about the speakers and their findings. We will highlight the take home message of each speech.

Marvin Caruthers - University of Colorado at Boulder

Marvin Caruthers is a distinguished professor of chemistry and biochemistry at the University of Colorado and is member of the National Academy of Science and the American Academy of Arts and Sciences. In the early 1980s, Professor Caruthers laid the foundation for the development of automated gene synthesizers, used by researchers for chromosome mapping, DNA sequencing, and the diagnosis of diseases and genetic disorders. He was most instrumental in the development of technologies that have led to the emergence of such notable companies as Applied Biosystems. He was also one of the founders of Amgen Inc. currently employing over 16000 people. He holds over twenty U.S. patents and his laboratory continues to develop new chemistries for synthesizing biological molecules and exploring their uses.

Speech: Cellular uptake of phosphonoacetate DNA- Synthesis of appropriate analogues

Summary: Caruthers gave an overview of the history of oligonucleotide synthesis entering in details of papers published by Khorana, Letsinger, Matteucci, Beaucage, Michelson, Ogilvie and himself. He ends with this question: Can PACE oligos carry a complementary RNA strand into cells? The answer is yes.

Christoph Rosenbohm - Santaris Pharma

Santaris Pharma is a clinical stage biopharmaceutical company focused on developing designer drugs for targeted therapy. We are pioneers in the field of oligonucleotide drugs based on our proprietary, 3rd generation RNA analogue, Locked Nucleic Acid (LNA). LNA transforms the therapeutic potential of such drugs, thereby substantially improving the prospect of developing successful novel drugs that can help patients live longer and better lives.

Speech: Locked Nucleic Acid: from discovery to first dose in man from a chemistry perspective

Summary: Santaris Pharma has exclusive rights to use the LNA Drug Platform to develop new classes of RNA medicines targeting mRNAs and miRNAs associated with disease. It is a good time to outsource the manufacturing of the material to other companies like Girindus.

Hagen Cramer - Girindus

Hagen Cramer, Ph.D., has worked in the field of oligonucleotides and 2-5A analogs since 1989 and has published 19 articles and has authored one book. Dr. Cramer received his PhD from the University of Konstanz, Germany in 1995 where he worked in the lab of Prof. Dr. Wolfgang Pfeleiderer. After completing his Ph.D., he joined Dr. Paul Torrence's group at the National Institutes of Health for post doctorate work on chemically modified 2-5A analogs. Before joining Girindus in 2005 he served as Director of Chemistry for Ridgeway Biosystems and as Scientific Director for Gemini Technologies.

Speech: Oligonucleotide manufacturing at Girindus

Summary: the major classes of oligonucleotides therapeutics are synthesized in Girindus using Solid Phase Synthesis: Antisense oligos, aptamers, immunostimulatory oligos, siRNAs, miRNAs.

Do you do anything different from other companies?
Why should one choose your company as a supplier?



Tad Wyrzykiewicz

Oligonucleotides synthesis has been in development for almost 30 years and for that reason a tremendous amount of intellectual properties has been generated in that area. And this has a very direct impact on freedom to operate and Girindus is extremely sensitive to that. Product development history and existing intellectual property may have profound impact on design of the manufacturing process. Girindus developed solid understanding of this area and knows that the freedom to operate is what makes the difference.

Jesper Wengel - University of Southern Denmark

Over the past 15 years, Professor Wengel has made many significant contributions to bioorganic chemistry. Particular areas of focus have been the synthesis and properties of modified nucleosides and oligonucleotides, and the use of branched and functionalized oligonucleotides within nanobioscience.

Speech: Locked and unlocked Nucleic acids

Summary: He displayed the several steps that occur from DNA to LNA and their analogues and focused on UNA.

Pat Limbach - University of Cincinnati

Pat Limbach is a bioanalytical chemist with research interests in mass spectrometry, ribonucleoprotein complexes and microfluidics. After earning an undergraduate degree from Centre College in 1988, he studied under the direction of Dr. Alan G. Marshall at The Ohio State University. While there, his graduate research focused on instrumentation improvements to Fourier Transform Ion Cyclotron Resonance Mass Spectrometry. He received his PhD from OSU in 1992. He then took a postdoctoral position at the University of Utah working with Dr. James A. McCloskey. While in Utah, he worked in the area of RNA chemistry and nucleic acid mass spectrometry. In 1995, he joined the faculty at Louisiana State University and was promoted to Associate Professor in 1999. In 2001, he moved to his current position in Cincinnati. He has received numerous teaching and research awards including the Young Investigator Research Award from the American Society for Mass Spectrometry and the Sigma Xi Research Investigator Award.

Speech: Mass-spectrometry challenges for ODN therapeutics

Summary: Goal: to characterize those molecules with modifications to their structure (excluding DNA and mRNA). The challenge: sample purification. Matrix-assisted laser desorption/ionization (MALDI-MS) and Electrospray ionization mass spectrometry (ESI-MS) were compared.

Masad Damha - McGill University

Masad José Damha was born in Managua, Nicaragua, where he graduated from "El Instituto Pedagógico de Managua (La Salle)" in 1977. He obtained his B.Sc. ('83) and Ph.D. ('88) degrees at McGill University, the latter working with Kelvin K. Ogilvie. Damha was awarded a NSERC postdoctoral fellowship in 1987, but declined the honor in favor of an Assistant Professorship at the University of Toronto's Erindale College. In 1992, he returned to his Alma Mater, where as James McGill Professor of Chemistry, he is involved in the synthesis and study of nucleic acids.

Speech: Modifying DNA's building blocks – Insights in nucleic acid structure and development of DNA/RNA therapeutics

Summary: Nucleic acid probes studied in his lab: 2'-F-ANA. FANA is a DNA mimic and is compared to DNA.

Sergei M. Gryaznov - Geron Corporation

Prior to joining Geron Corp, Dr. Gryaznov was with Lynx Therapeutics Inc, from 1993 till 1997, as a Research Fellow, and from 1990 till 1993 with Prof. Robert L. Letsinger at Northwestern University, as a Post-Doctoral Fellow and as a Visiting Scientist. He received his Ph.D degree in nucleic acid chemistry in 1987 from M.V. Lomonosov Moscow University (under Prof. Zoe Shabarova), and then worked as a Research Scientist with Prof. Eugene Sverdlov at M.M. Shemyakin Institute of Bioorganic Chemistry in Moscow, Russia.

Speech: DNA and RNA mimetics: oligonucleotide N3'-> P5' Phosphoramidates

Summary: Oligonucleotide N3'-> P5' Phosphoramidates is demonstrated to act as antisense agent in various cellular and animal model systems. GRN163 can circumvent blood-brain barrier and effectively enter GBM tumours via olfactory system.

Andrew Vaillant - Replicor

Chief Scientific Officer and Director of Operations at Replicor. He is responsible for all technology assessment and research activities at Replicor. He supervises and directs all internal and outsourced scientific activities and is a co-inventor of REP 9AC. He previously held positions in two biotechnology companies. He holds a Ph.D. in Cell Biology and a B.Sc in Biology (Summa Cum Laude) from the University of Ottawa.

Speech: Phosphorothiate oligonucleotides as amphipathic polymers: mechanistic properties and therapeutic application in the treatment of viral hepatitis

Summary: Amphipathic DNA polymers are antiviral agents. This activity is due to amphipathic characteristics not to antisense activity. The antiviral action of REP9AC is considered against HBV.

Fran Wincott - Wincott & Associates

Dr. Fran Wincott is President of Wincott & Associates, LLC, a consulting firm focused on providing assistance in the area of oligonucleotide manufacturing and development. Prior to founding Wincott & Associates, Dr. Wincott was Vice President of Oligonucleotide Manufacturing & Development at Eyetech Pharmaceuticals, Inc. In that capacity, she was primarily responsible for the successful validation of a commercial oligonucleotide manufacturing process, of significant importance in the approval of the Macugen NDA and commercial launch. Prior to joining Eyetech Pharmaceuticals, Dr. Wincott served as Senior Director of Manufacturing Operations at Ribozyme Pharmaceuticals, Inc. (now Sirna Therapeutics a subsidiary of Merck, Inc.).

Speech: Manufacturing therapeutic oligonucleotides; lessons learned from Macugen

Summary: Taking example from Macugen, one of the two oligo drugs approved up to now, a few advices are displayed on how to manufacture therapeutic oligos: the most important things to take into considerations are Analytical methods – you have to ensure suitability – you can't scale up if you haven't got a suitable analytical method, regulatory authorities and of course keep updated – methods change over time.

David Konys - Alnylam

David Konys joined Alnylam in April 2003. He was formerly Vice President of Corporate Development at Ingenium Pharmaceuticals AG, and prior to that, had over 15 years of experience at Biogen, Inc., where he was the 1995 recipient of the Chairman's Award. During his career, Mr. Konys has been responsible for a wide array of activities related to the building and expansion of growing biotech companies, including intellectual property management, facilities expansion, marketing, and licensing.

Speech: Cationic Delivery systems

Summary: The main issue is how to turn siRNAs into drugs. An example was displayed on how siRNA can treat liver cancers thanks to the development of new materials for siRNA delivery (liposomal nanoparticle formulation).

David W. Wilson - Girindus

David W. Wilson David started his industrial career at Great Lakes Chemicals Company before starting at Girindus America in June 2000 in their Chemical Development group. His work at Girindus was focused on process development of laboratory scale processes for scale up to the pilot plant for early phase clinical Small Molecule API's and he was promoted to Section Head in 2002. In June 2005, David was promoted to Production Supervisor for Small Molecules where has supervised both the Chemical Development and Pilot Plant. In his tenure at Girindus, David has been involved on numerous programs in overcoming the many obstacles involved to develop a chemical process.

Speech: Synthesis of components for cationic lipid delivery systems
Summary: Girindus Small molecules has worked in collaboration with Alnylam for the GMP release of their TETA-5LAP for use in the cationic delivery program.

Kelvin Ogilvie - Acadia University

In graduate school, Kelvin Ogilvie became determined to find a way to chemically synthesize RNA. More than 20 years later, he succeeded in synthesizing the RNA molecule that initiates protein synthesis in living cells. Along the way, he developed a new class of anti-virus molecules, produced the critical ingredient in the life-saving drug Ganciclovir and invented an automated DNA synthesizer that made industrial oligonucleotide production practical.

Speech: Nucleotide synthesis- The first forty years 1950-1990

Summary: Historical highlights were displayed: the Watson and Crick dogma, the main challenges (protecting groups, coupling, retrieval of product, how to do a Merrifield), the first explorers (Lord Todd – synthesis of dinucleotide; Khorana – the development of protecting group and in 1972 the first total gene synthesis; Letsinger – the triester method; Eckstein & Rick; Reese); challenges achieved to the end of the 60's (Triester concept accepted, protecting groups, stability of internucleotide linkages & glycoside bonds, solid phase synthesis), the great advances of the 1970's (automation – Van Boom; long oligos via triesters – Narang and Reese; the phosphate triester approach – Letsinger; solid phase synthesis; DNA synthesis – Letsinger; peptide Synthesis- Bruce Merrifield; Polyesterene – Ogilvie & Kroeker; solid impermeable system – Koster; glass beads – Tundo; RNA synthesis – alkyl silyl protecting groups – Ogilvie), the 1980's (Letsinger method makes everything possible; DNA automation – Ogilvie; 1981 – Launch of the first gene machine: DNA was going to be available!; continuous synthesis of transfer RNA; combination of DNA and RNA – Serge Beaucage, Grad student of Ogilvie).

*Do you do anything different from other companies?
Why should one choose your company as a supplier?*



Mark Laskovics

Girindus has valuable licences in the manufacturing area that we got from developers of the technologies. So we actually are in the position to commercialize oligos without the threat of litigation. Second thing: we have done our own research and we have also other technologies that are used on this solid phase synthesizer that do not infringe anyone's patents. So we have several options for applying solid phase technology to the clients programmes to ensure that there will be no litigation, that their programme is not slowed down by any infringement. Therefore we have a good relationship with the developers of those technologies. And this is what differentiates us from other companies.

During the Symposium several events took place and we are pleased to report them. After the keynote speech of Caruthers on the first day a Commercial Collaboration Agreement between Girindus and RiboTask was signed. Under the terms of the agreement, RiboTask, a Denmark based company founded by Prof. Jesper Wengel and Suzy Lena, Chief Executive Officer of RiboTask, will gain access to the worldwide sales and marketing team of Girindus, and Girindus through the collaboration with RiboTask will have the ability to offer its customers seamless manufacture of a wide variety of oligonucleotides from the mg quantity to commercial kg quantities. "Prof. Wengel, Chairman of the Board of RiboTask, has long been recognized as one of the leaders in the oligonucleotide field" stated Mark Laskovics. "And RiboTask has been built into a world-class organization to provide a range of oligonucleotides, particularly oligonucleotides possessing complex sequences. We are delighted that our two organizations will work together to provide the best possible solution for our customers", he concludes. "We have seen in Girindus the technical and financial staying power to be the pre-eminent force in the oligonucleotide field," stated Prof. Wengel. "We are delighted to enter into a partner relationship with Girindus!". During the lunch break of the first day the new oligonucleotide facility of 5.2M\$ investment was unveiled and Girindus representatives, the local government and keynote speakers participated in the ribbon cutting. Participants had the opportunity to have a look at the plant and obtain some information. The facility was constructed in year 1993, in 2007 it received a FDA inspection and, after Solvay became the major shareholder in 2005 and with the support of the local authorities, it was modified to its current state. Tad Wyrzykiewicz gave us some information on this facility.

"In our facility we currently have three independent trains. Within each train we have precisely matched synthesis, purification, desalting and lyophilisation equipment. The small scale train can synthesize up to 8mmol per synthesis batch. Usually this train is used for early stages and in projects where you don't need a lot of material. We have another train, so called medium range train, which can handle projects up to 60mmol/scale. As a rule, depending on the project, we can expect to synthesize in a range of 2-4 grams of pure product per 1mmol of synthesized scale. So the synthesis of 60mmol could lead to 120 -240g of product per batch. That is why this train

is usually satisfactory for most projects. We have also a large scale train capable of synthesizing up to 120mmol/scale. This train is part of our current expansion. At the end of the two days' Symposium "the Wall of Fame" was unveiled and 6 images were displayed as the six milestones of the history of oligonucleotides. Of course the first one was in honour of Watson and Crick, then Khorana, Letsinger, Ogilvie, Caruthers and finally Girindus. Girindus of course aims to represent a future milestone in the field of oligonucleotides manufacturing and we hope this will come true. At the very end of the symposium there was the presentation of inaugural "Girindus Leader in Oligonucleotides" award which was given to Caruthers who received it from his former student Tadeusz Wyrzykiewicz who acknowledged him as his mentor. Together with the award Caruthers received a donation from Girindus of 1 thousand dollars addressed to the Island School where Caruthers holds his chair. The ceremony was very touching and ended with a toast at which everyone in the room participated.

We can certainly state that the symposium was a great success both from the scientific and humane point of view. The science of course is not under discussion but what Girindus managed to do other than the symposium itself was to create a unique atmosphere among the participants. Thanks to the extra activities organized by Girindus and its staff it was possible to meet experts from different companies and countries in a friendly environment. Moreover the decision to have a restricted number of participants allowed people not only to know each other for a few minutes – as usually happens on these occasions – but to deepen their acquaintance from a personal point of view.

I would like to thank Girindus for this extremely interesting experience and I am sure I will hear more about this company on the occasion of the launch of a therapeutic oligonucleotide by one of its clients.

REFERENCE

1. R. Hogrefe, "A short history of oligonucleotides synthesis", Trilink, Biotechnologies. 

