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Workshop Report

Synthesis and the organism: biology, chemistry, and engineering

Dominic J. Berry

Report and analysis of an interdisciplinary workshop that took place on 28 November 2017.

Organised as a collaboration between the Engineering Life project (ERC 616510-ENLIFE), the Flowers Consortium (EP/J02175X/1) and the Chemical Heritage Foundation.

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The views expressed in this publication are those of the workshop participants and the author. Institutional affiliations are provided for purposes of identification only and do not imply endorsement of the content herein.

We would like to thank all the workshop participants for their contribution to the constructive and engaging discussions and for their contributions to the review process. My considerable gratitude to Dr Dmitriy Myelnikov for designing and producing this report to such a high quality, particularly as this is now the second of our reports to which he has dedicated his skills. The first, authored by Deborah Scott and Dominic Berry, *Genetic resources in the age of the Nagoya Protocol and gene/genome synthesis*, can be found at the Engineering Life project website:

www.stis.ed.ac.uk/engineeringlife

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None of the participants in the workshop should be considered as committed to the arguments and views contained herein.

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Introduction from Engineering Life and the Science History Institute

Jane Calvert

Engineering Life

This workshop on the history of DNA synthesis was one of a series of interdisciplinary workshops organised by the Engineering Life project. The project investigates the movement of ideas, practices, policies and promises from engineering into the life sciences. Its focus is on synthetic biology, a field that aspires to engineer biological systems. Although DNA synthesis is essential to synthetic biology, it often remains in the background in discussions of the field. By bringing it to the foreground this workshop contributed to the Engineering Life project in several ways. Importantly, it provided a new way of thinking about the history of synthetic biology, which often traces its origins to the early 2000s, when its engineering agenda was articulated. Focusing on synthesis allowed us to connect synthetic biology to a much longer trajectory of DNA synthesis, starting in the 1950s. The workshop also highlighted the importance of chemistry, alongside biology and engineering, in DNA synthesis and in synthetic biology more broadly. It also raised challenging questions about the differences between synthesized and non-synthesized DNA; about the importance of provenance, inheritance and genealogical relationships, and what happens when these are bypassed by chemical DNA synthesis. Relatedly, thinking about the distinctiveness of synthesized DNA drew our attention to the nature of DNA itself. Synthesis produces a material entity, a molecular sequence, but DNA is more than this in also being a carrier of information and a product of evolution. By foregrounding these historical and conceptual dimensions of DNA synthesis the workshop allowed us to think afresh about current large-scale whole genome synthesis projects involving yeast and human genomes. Finally, I would like to say how valuable it was to hold the workshop at the Science History Institute, where the unique historical expertise in chemistry, engineering and the life sciences greatly enriched our discussions.

Jody Roberts

Science History Institute

The Science History Institute was proud to partner with the Engineering Life project team at University of Edinburgh to make this unique workshop possible. At the core of our institution's mission is creating tools to make the past accessible in ways that can foster important conversations across constituencies about the place of science in our society. As the Chemical Heritage Foundation has morphed into the Science History Institute following its merger with the Life Sciences Foundation, we are particularly excited about occasions for highlighting and examining the connected histories of these molecular fields. The history of DNA synthesis provides an almost perfect exemplar for charting out new directions for collections, knowledge production, and public engagement about these critical breakthroughs that continue to impact all of our lives.

The workshop focused on an often forgotten or overlooked aspect of laboratory science: the role of new instrumentation as a driving force for breakthroughs. The presentations and conversations at this workshop traced the ways in which laboratory technique becomes codified in an instrument; how the commercialization of an instrument transfers skills and capabilities to users across new geographies; and how this mobilization of users yields the sort of breakneck breakthroughs that have come to define contemporary discourse in and about synthetic biology and biomedical research. By convening a group of practitioners, observers, and researchers from fields in and around synthetic biology, we simultaneously captured the before and after moments of instrumental development and caught a glimpse of how this technology continues to shape how and where research is done, what questions can be explored, and what might become possible in a not too distant future. In settings such as this it's natural to ask the question: how will this history be preserved? We were delighted to facilitate a process of discovery connecting our museum at the Science History Institute to the participants of this workshop to begin what is always a long process of imagining and then initiating a collecting initiative that can serve as a representative collection of this work. On behalf of the Science History Institute, I am delighted to have had the opportunity to collaborate with the Engineering Life project. Their work has created an uncommon space for thoughtful deliberation, inspection, and perspective needed for finding aligning emerging science with social needs.

Executive Summary

This workshop attended to the ways in which methods for the chemical synthesis of organic materials has mattered, and continues to matter, for biological science and technology. It adopted a fundamentally historical approach with a focus on the synthesis of DNA, and was informed by accounts from scientific practitioners, social scientists, museologists, philosophers, and historians. The workshop's investigation was inspired by a focal point: the efforts of a small international community of scientists and engineers who from around the 1960s picked up the challenge of synthesizing nucleotide sequences without having to rely on finding desired sequences in existing organisms. This was the making of sequences through chemistry, technology and engineering. While the historiography of biotechnology is vast, the capacity for DNA synthesis itself has largely gone unnoticed, the vast majority of work focusing on techniques for recombination, its meanings, broader social significance, and reception amongst diverse publics. By staying focussed on the particularities of biological molecules as *synthesised* the workshop aimed to break new ground, drawing in material culture, engineering studies, and their historical, philosophical and sociological intersections.

While DNA synthesis was the focal point, these activities needed to be understood in a longer and broader context, right up to the present. Speakers accordingly focussed on a range of periods, and highlighted different features when it came to synthesis and the organism, each with an emphasis on different kinds of scientific, commercial, or organic actor. Indeed it is no doubt thanks to the diversity of the kinds of actor involved that scholars in the history of science have yet to grapple with the cases addressed here, the majority staying within either chemistry, biology, or engineering. This workshop recognises that synthesis sits in an uncomfortable research space for historians and philosophers of science. It was dedicated to addressing this discomfort and producing materials for the systematic international investigation of nonbiological, or perhaps 'mechano-chemical' DNA synthesis, the philosophical questions it provokes, the historiographical revisionism it invites, and the social relations it changes.

Part 1 of the report incorporates short summaries of the papers given (each of which was 20 minutes in length) and reports of the question period. Part 2 includes the biographies of our participants. In an annex we include copies of the workshop documentation. For the author of the report the following themes seem to deserve particular attention:

1. Decomposition and recomposition

At various different points in the history of science, experimenters have been prompted to celebrate the strategy of repeated rounds of analysis and recombination, followed by further analysis and further recombination. In biology for instance we might think of William Batesons' analogies between decomposition and recomposition in chemistry and the same practices in genetics, or Wilhelm Johannsen's emphasis on the usefulness of composing and decomposing pure lines to understand heredity. From a very abstract perspective, one devoid of any specific experimental content, it can be difficult to distinguish between all the different kinds of epistemic strategy that marry together induction and intervention in this way. For instance, is there anything additional implied by the 'bottom-up' approach in minimal cell research, or the 'design, build, test' cycle emphasised in synthetic biology, beyond Francis Bacon's sixteenth century commitment to combining 'works of fruit' with 'works of light'? The extreme and ahistorical nature of this juxtaposition is intended to puncture much of the inflationary rhetoric used by present proponents of particular experimental designs.

What we learn from the papers presented in this workshop, is that arguments about the epistemic value of decomposition and recomposition must first be made meaningful through the specifics of the material being decomposed and recomposed. A focus on the specifics of DNA, what it does, where it comes from, its various roles in experimentation and analysis, is a methodological commitment that also allows us to analyse and assess broader experimental designs and epistemic strategies that are argued to relate to them. Obviously this kind of methodological commitment can be extended to materials well beyond DNA.

2. Values and value making

Throughout the workshop different speakers made different claims as to what things were valuable, or became valuable, and introduced different kinds of value, from financial, to social, experimental, moral, and many things in between. The making of DNA and its becoming an experimental commodity is therefore at one and the same time a

Fig. 1. *Left to right:* Dr. Jody Roberts (Director of Science History Institute's Institute for Research and managing director of SHI); Dr. Dominic Berry (Research Fellow, Engineering Life Project); Marv Caruthers (Distinguished Professor of Biochemistry and Chemistry at the University of Colorado, Boulder and pioneer in DNA synthesis); Dr. Robert G. W. Anderson (President and CEO of Science History Institute), in the biochemistry and biotechnology section of the SHI museum. Thanks to Samantha Blatt of the SHI for taking this photograph and thanks to the SHI for permission to use it.

history of making values. In this respect the history of DNA synthesis can be immediately related to ongoing research on values and valuation, historical interpretation of the relations between science and technology and economic change, public and private property, intellectual property, and cultures of innovation.

Remembering that different stakeholders will have different conceptions of what is valuable, and what can be valuable, provides excellent grounds for the motivation of historical research and analysis. Indeed a communities' responding to and learning how to value material-semiotic objects is often at the heart of an historical enquiry. Being explicit about this opens up interdisciplinary paths between historical and social scientific research, while providing richer materials for histories of the sciences. It also further emphasises the need to draw in a wide range of stakeholders, including scientists, industrialists, economists, social historians, civil society, and so on, all of whom will have their own views as to what is valuable, most valuable, and why.

3. The history of biology meeting the history of technology

The intersection of the history of biology and history of technology has been subject to considerable renewed attention in recent years. At present historians trained in each subject are increasingly learning how to apply their historiographical approaches to cases thought to lie outside their primary, perhaps even appropriate, research contexts. DNA synthesis provides an ideal case study for those contributing to or skeptical of this agenda, for it is impossible to tell its history without addressing biology and technology (and chemistry and engineering) simultaneously. How historians can and should respond to these kinds of context is currently being debated, and DNA synthesis can provide a range of provocations.

To different people DNA is an experimental tool, epistemic object, commodity, chemical and physical and biological material, natural resource, economic resource, political arena, and many more other things that we commonly only research through attention to its recombination. By attending to the fact that there are different methods for the *making* of DNA, we can grasp the different meanings of its making, and revise history accordingly.

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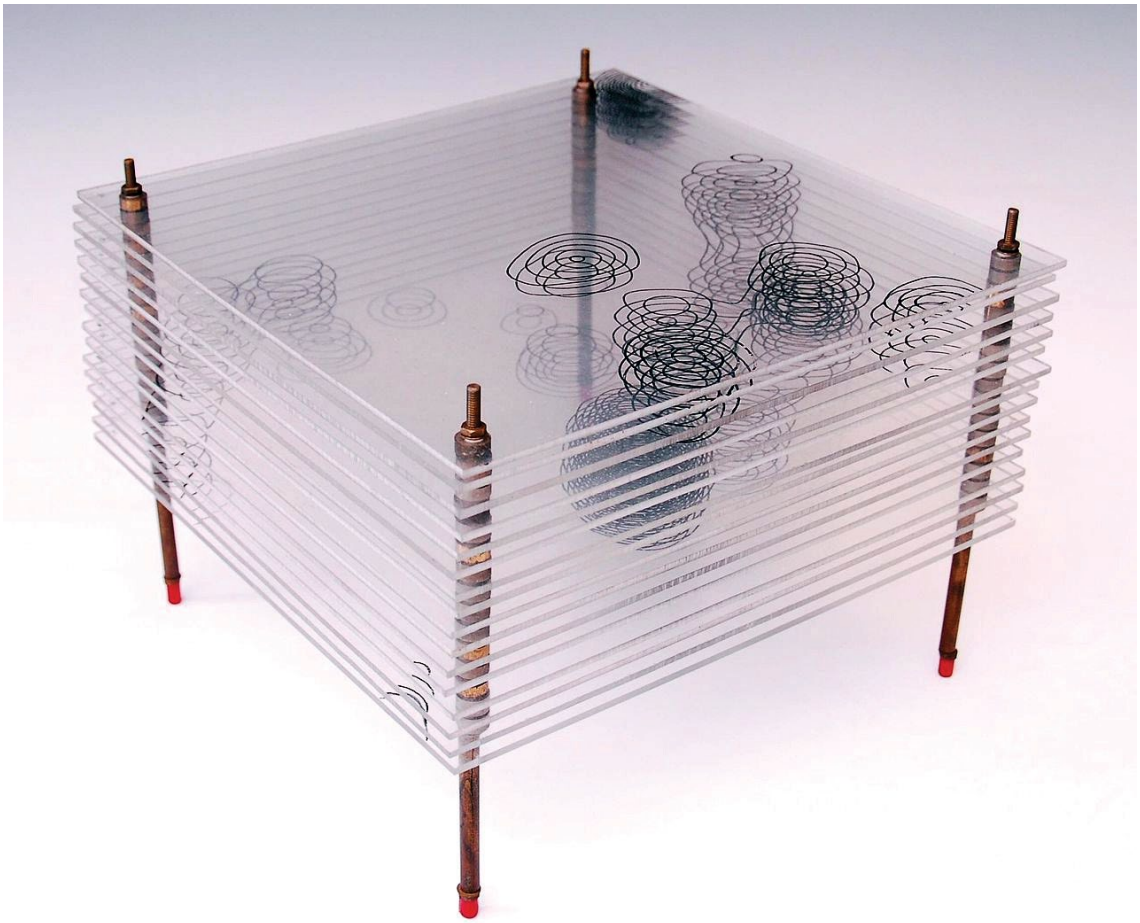

Fig. 2. Model of the Structure of Penicillin, by Dorothy Hodgkin. By Museum of the History of Science, University of Oxford [CC BY-SA 3.0], via Wikimedia Commons.

Session 1: Introduction to the Worskhop

Dominic Berry

Introduction

This workshop constitutes part of the Engineering Life project, which is run by Prof. Jane Calvert in Edinburgh. We are an interdisciplinary team of researchers, including social scientists, geographers, historians, all of us with quite different backgrounds, dedicated to researching contemporary science as it is practiced in the present. The broad umbrella that we are interested in is biological engineering, and within that, we are particularly interested in studying synthetic biology: trying to understand what's going on with that range of sciences, the developments underway, and the ways in which it is significant for broader society. For myself, as a historian of science, my role on the project is to try and historicize contemporary science, to try and bring history to synthetic biology, and in the process bring the value of the history and philosophy of science to the present. For me that is all that this

workshop is made of and dedicated to, trying to explore the past in order to better understand and appreciate the present.

One important thing to recognise about our workshop today is that it is deeply interdisciplinary. We have people from a whole range of backgrounds, interests, expertise, their own reasons for finding something like DNA synthesis interesting. That interdisciplinarity is important for at least two reasons. One, the phenomena that we are all here to discuss, DNA synthesis, is itself a deeply interdisciplinary phenomena. There were lots of kinds of actor involved, and lots of different expertise involved. Another reason to make this an interdisciplinary event, is that there is lots to do! We need as many people as we can get in order to pool together this history. So I hope from our discussions we can learn what kinds of institutions we want to go and investigate further, which archives to try and find, which people to try and follow up, who we need to convince to leave their papers to an archive, to build the archive that we need. Another question that is close to the heart of the Science History Institute, is what kinds of objects we might want to collect in order to preserve the material history of something like DNA synthesis. I am hoping we can get lots of ideas here. When you take a topic like DNA synthesis, we have the opportunity to think large and be ambitious about what we want to do with that history.

Not everyone here is used to thinking historically, and those of you that are, we don't all think historically in the same way. So with the rest of my introduction I want to give you an insight into how I, myself, understand historical change, and the kinds of history that I see today contributing to. Not so that I can convince you it's the right one, but so you can appreciate some of the quirkier aspects of the workshop. In order to do that I am going to lean on an analogy from the history of x-ray crystallography.

When Dorothy Hodgkin was working on the structure of penicillin, she adopted the practice in x-ray crystallography, of mapping out the data on sheets of perspex. These would then be layered one on top of another, allowing you to look *through* the perspex, eventually coming to appreciate what the 3D structure must look like. I think this helps as *analogy* to visualise my understanding of historical change. But what are we trying to understand the structure of, what is our penicillin?

The history of DNA synthesis is at one and the same time chemical, biological, technological, and engineered

There are some interesting questions about how to actually describe the topic of our workshop. Is DNA synthesis right? I have proposed mechano-chemical in the workshop proposal, in order to recognise the variety of features that make this kind of synthesis distinct from what is going on in cells, but what do you think of that? For lots of purposes today we are going to be able to say synthesis or chemical synthesis, but does that capture everything going on in those instantiations, and are there other interpretations? It's also the case that perhaps we are actually wanting to talk about something else, and the synthesis frame ultimately does not work. One could have easily organised todays workshop around 'model organism research and biotech', with DNA synthesis becoming one amongst a number of technologies that mattered, or we could have gone for 'histories of the commercialisation of university research', and again DNA synthesis would have become one of a number of examples.

Why chose DNA synthesis then? Well if you're part of a project focussed on synthetic biology, then DNA synthesis is a very quick way to start forcing some history into contemporary practices, because synthesis is essential to everything that synthetic biologists get up to. So if we can learn more about the history of DNA synthesis we are *de facto* learning about the history of synthetic biology, even if it is not necessarily on the historical terms that synthetic biologists understand themselves. Another reason to choose this focus, is that in terms of the history of biotechnology, DNA synthesis has been neglected, even though it does come into parts of stories that are very well known, such as the

Human Genome Project or PCR. DNA synthesis has not had this kind of dedicated attention that we're going to give it today. The time is ripe for people to start doing so, drawing in people who have been working in fields associated with DNA synthesis, and start collecting the materials that we would need in order to preserve it. Lastly, I think this approach to the topic sets us up with some nice historiographical challenges. The history of DNA synthesis is at one and the same time chemical, biological, technological, and engineered. As good as the discipline of the history of science is, it is not necessarily good yet at dealing with that kind of historical space. So another reason to have this workshop is to produce materials that will make such an exploration easier for other historians in the future.

Returning now to Hodgkin, I want us to be thinking of those perspex sheets, layered on top of one another, and the overall structure that emerges, as we try and piece together a history of DNA synthesis. We are perhaps trying to find ways to perform x-ray crystallography on the past, at least, that is an image that feels right, to my mind, as being close to what it is to think historically about a subject. Some of the parts of the structure will be directly connected, other parts disconnected, other parts meeting for a while before going off to have lives of their own. But you come to grasp the whole by putting everything into place.

Session 1: Whole genomes/organisms

Alok Srivastava & Elihu M. Gerson

Synthesis of Viable Genomes and Organisms: Understanding Wholes

What do synthesis experiments add to our understanding and our capacity to explain things? How new kind of work do synthesis experiments do? Similarly, a parallel question is what do synthesis experiments add to technology and how do they do it? In this paper, I focus on a particular class of synthesis experiments called Total Synthesis projects. I will discuss two cases and in both of them, I will use the standards of total synthesis projects as practiced by chemists to elucidate their contributions.

The Nobel Prize-winning chemist Gobind Khorana highlighted the integrative nature of working on chemical experiments in biology in the opening sentence of his Nobel lecture: "Recent progress in the understanding of the genetic code is the result of the efforts of a large number of workers professing a variety of scientific disciplines." (He received the prize in 1968 for his work on "interpretation of the genetic code and its function in protein synthesis.) For myself what matters here is the idea of individual researches professing and practicing a range of scientific disciplines and thereby synthesizing those disciplines.

I will be arguing that synthesizing does more than explaining; explaining and making both develop capacities for pulling systems apart and putting them back together; and that making is more than manipulating. When it comes to making the chemist holds a different standard than the one that biologists have typically adopted. That making is more than manipulating and is a way to reconcile two different kinds of complexities: descriptive complexity, and interactive complexities. By descriptive complexity, I mean that explanations and mechanisms delineated in the same phenomena by different disciplines do not easily coincide. For example, for the gene, the informational picture, the chemical biosynthetic picture, and the physiological picture don't line up by themselves—like Dorothy Hodgkin's perspex sheets do. By interactive complexity, I mean that the explanations and mechanisms work across multiple dimensions of explanation. For example, the chemi-synthetic picture of the gene is only a subset of the full phenotype generating aspect of the physiological gene referred to by the geneticists. These descriptions and explanation *can* line up in

practice if the independent diagrams we hold bring you to do something new in the lab, but those diagrams themselves can't line up one on top of each other to be part of the same whole.

Before I begin, I also need to explain the particular standing of total synthesis experiments and projects in contrast to synthesizing a part of a whole or demonstrating the mechanistic operation of a part. Experiments demonstrating the complete chemical synthesis of biologically viable wholes such as genes and genomes are examples of Total Synthesis experiments. Total synthesis projects are a long-standing institution in the professional world of chemists and have been adopted subsequently by biochemists, molecular biologists and most recently by synthetic biologists. This has been applied to DNA, biosynthetic pathways, biochemical complexes, genes, regulatory pathways, and now genomes, with the hope of getting to organisms. One of the points of the talk is to distinguish the claim of synthetic organisms versus synthetic genomes. What this synthesis means is different according to the type of scientist involved. Biochemists hold themselves to having reconstituted purified components that comprise DNA polymerase activity or RNA polymerase activity. Molecular and cell biologists they reconstitute complexes *in vivo*. And synthetic biologists are taking it to recompose whole systems.

In this talk, we also want to introduce two distinct types of coordinative arrangements entailed by the work of assembling parts into viable wholes—scaffolds to hold the organization of parts while under construction and brackets to hold together parts or capacities that are not linked but must operate near each other.

I will be working with two cases of total synthesis projects. First is the accomplishment in 1979 of the Khorana lab demonstrating the first total synthesis of a gene and showing its biological activity. The other is the claim from March 2016 of the total synthesis of a minimal genome—they are careful to avoid saying 'organism', but do the chemist's standards of total synthesis projects allow such a distinction

Making is more than manipulating and is a way to reconcile two different kinds of complexities: descriptive complexity, and interactive complexities.

between the material entity and its biological behaviour? The Khorana lab successfully demonstrated a reconciliation of the chemical gene, the informational gene that Francis Crick would recognize, and the physiological gene that even Thomas Hunt Morgan might recognize. In comparison, what kinds of reconciliations were attempted by the Venter Institute's project? Their goal was to produce the minimum viable organism as defined by the minimal genome, the minimal set of cellular parts and pathways and the minimal physiological capacities required to keep a cell viable. These three descriptions and mechanisms—genome, parts and pathways, and physiological capacities—needed to be defined exactly and reconciled in their project. The second half of the discussion will attempt to delineate the accomplishments and limitations of their attempt.

There are at least three aspects of total synthesis work. The first is articulating established explanations and manipulation techniques from decomposition studies i.e. pulling things apart and saying 'this thing caused that'. In this aspect, you are putting the pinch points between your manipulations and explanations to say 'we have mechanisms here that we can work with and recapitulate what nature does.' Second, you need to show that once your identified parts are recomposed, they behave as expected. Third, when the target phenomenon has multiple dimensions you have to reconcile different explanations, and the associated manipulations and mechanisms, in order to show your perspective is complete. In the case of Khorana and the gene, the informational, chemical and physiological dimensions of the gene were reconciled in the total synthesis project.

The Khorana Lab combined tools from chemistry and biochemistry. The direct chemical synthesis was done to obtain the small oligonucleotides, but enzyme-based

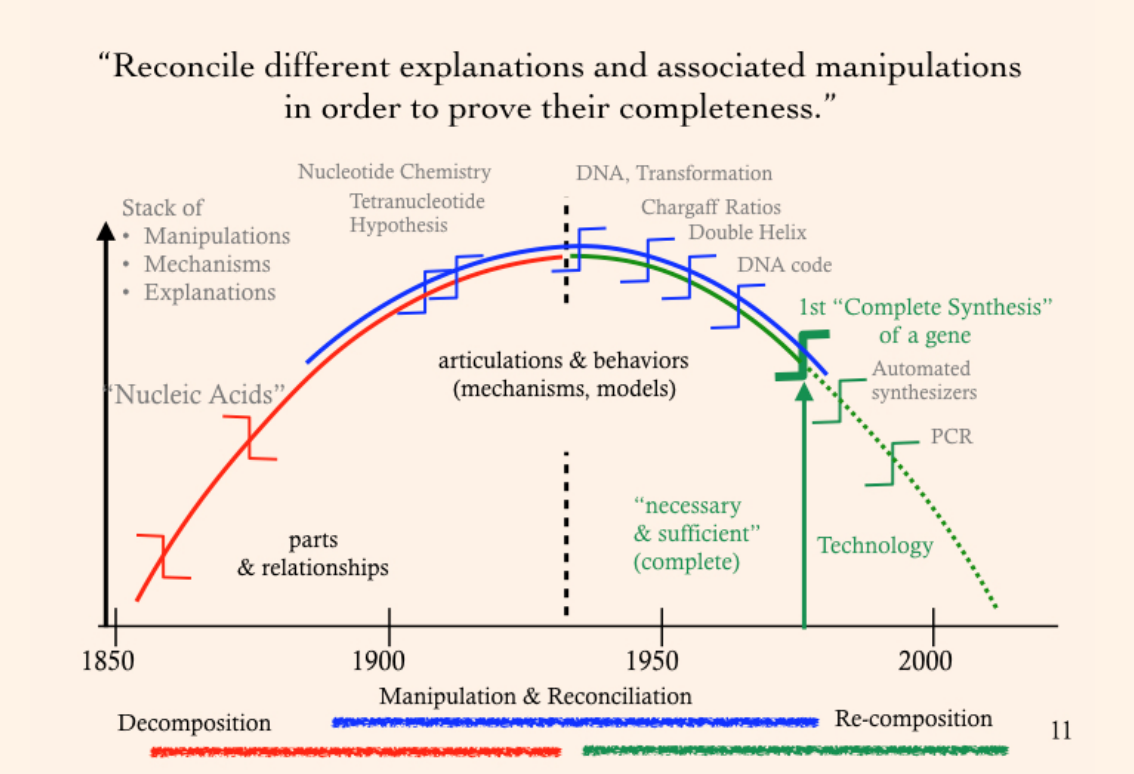

Fig. 3. Visualisation of a historical arc showing passage through stages of decomposition, manipulation and re-composition. Copyright retained by Alok Srivastava and Elihu M. Gerson.

biochemical reactions were used in the construction of the longer length DNA of the gene. And also the complementarity of duplex DNA was used to bind pieces with each other in the correct order to construct the whole length gene. Khorana called their method the chemical-enzymatic method for synthesizing the gene. Through several stages, the whole gene is assembled—and in their diagram, they depicted each location where enzymatic activity is completing the synthesis with a bump. To demonstrate the expected behavior of the gene they inserted the synthesized gene into a disabled version of its home organism—a bacteriophage (bacterial virus) lacking a copy of this essential gene. This disabled version of the bacteriophage is unable to complete the final stage of its life cycle in bacteria—to break out of the cells—which is visualized through the formation of plaques on a lawn of bacteria. The synthetic gene successfully restored plaque formation behaviour and reversed the disability of the bacteriophage.

The execution of a Total Synthesis project of a target phenomenon also marks a historical transition in development and integration of the multiple disciplines developing explanations and manipulations of that target phenomenon. This historical arc shows the passage from a phase of decomposition work into a phase of re-composition work through a transitional phase of reconciliation work. The decomposition phase accumulates discoveries of parts and their inter-relationships into a stack of possible explanations and manipulations. During the reconciliation phase, this stack of explanations and manipulations are rationalized with respect to the assembly of the whole and its behaviour. As the elements of this stack begin to fit together some of the explanations are found to be lacking and are replaced and some of the missing manipulation capacities are specified and discovered. As the elements of the stack begin to fit with each other the total stack reduces. The successful execution of the Total Synthesis Project marks a reconciled and complete repertoire of explanations and manipulations. The first total synthesis of a gene and the demonstration of its biological behaviour reconciled the

chemical, informational, and physiological explanations and manipulations of the gene. This full package of repertoires of manipulations underlying such a demonstration is portable and transportable. In this aspect, the successful execution of a total synthesis project of a whole marks the passage through a bottleneck in technology development. The tour-de-force efforts offer to all the workers in related disciplines a complete circuit of explanations and manipulations for the making and remaking of genes at the chemical level and the behavior of genes at the biological level.

Historically, the first successful total synthesis of a gene depended on an array of earlier completed work produced by a range of different disciplines. We might list the central dogma of molecular biology, gene structure, physiological activities of the cell, and chemical-enzymatic characterizations of the cell's proteins as capacities available to this project. Importantly also, the chemical-enzymatic explanations and manipulations of processes such as DNA polymerization and RNA polymerization had already been worked out in in-vitro & cell-free experiments before this project. These repertoires offered the starting stack of explanations and manipulation at the start of the reconciliation work involved this total synthesis project.

Reconciliation work during re-composition and re-assembly projects emphasize the role of unique classes of capacities called scaffolds and brackets. These are coordination devices to enable work within and across multiple levels of the phenomenon. This coordination includes the social level of the lab personnel and interacting disciplines and the physical level on the lab workbench and the test-tube. Scaffolds are required while a configuration of target phenomena is being assembled. Suitable scaffolds that hold the configuration together during and through the intermediate stages of assembly. The capacities of the scaffold are not built out of the mechanisms inherent in the phenomena but are recruited from outside such as the laboratory environment. In the Khorana case, a range of ways to hold the sequence of the gene together was utilized, such as the written sequence of the gene, the maps, and protocols used to represent the arrangements of the intermediate parts and to guide the sequence of assembly.

In the Khorana case, a range of ways to hold the sequence of the gene together was utilized, such as the written sequence of the gene, the maps, and protocols used to represent the arrangements of the intermediate parts and to guide the sequence of assembly.

Brackets, on the other hand, are used to hold capacities together when they are needed in the same space or time. Some capacities of the elements of a whole interact and need to be kept in place but blocked from interacting during assembly and some capacities that are not linked need to be kept together so that their joint action can drive the assembly. These situations are articulated with brackets. An example is the role of blocking chemistry in these experiments to deal with the many active centers in a chemical part of a polymerization reaction. Blocking agents being added to selective sites of a molecular part in one reaction to selectively enable a specific reaction and sequentially removed in subsequent reaction steps to enable other specific reactions are examples of brackets employed during bench-work. This class of coordination devices articulating DNA Synthesis in the laboratory has been a critical technology in the growth of DNA synthesis and it was crucial in the development of the capacities packaged in automated-mechano-chemical DNA synthesis.

Now turning to the Venter study. Their claim was that they had designed and synthesised a minimal genome. The intended goal of their project was to design and demonstrated a minimal and completely defined cellular organism. They aimed to achieve and demonstrate a reconciliation of three intersecting models and mechanisms of the minimal viable genome: the minimal set and network of genes, the minimal set of cellular parts and pathways

and the minimal physiological capacities of the cell.

An early accomplishment of the Venter Institute was to achieve the capacity to build genome length molecules of DNA from small pieces in surrogate chemical and biological environments. They also accomplished the ability to replace the native genome molecule of a host organism with the synthesized genome and re-boot the physiological life of the host cell with the transplanted genome. To achieve this the Venter laboratory behaves like a surrogate cell and is organized to take on several steps carried out by the cell. Several parts and sub-assemblies having to be specified, organized and held correctly along the step-wise process of making and piecing them together. The lab here is made up of a system of scaffolds and brackets that let it substitute for cellular processes. The Venter Lab acting in this manner as a surrogate cell is able to routinely specify, make and assemble a full bacterial genome, transplant into the host cell and reboot its physiological activity, all in three weeks.

However, in their pursuit of minimizing the list of parts and capacities to support a minimal organism the Venter group hit significant failures. The implemented genomes based on previous work from top labs such as the George Church group defining the minimum list of genes and pathways to support a cell. This minimum gene set included 166 genes and the transplanted organism did not reboot and could not be enlivened. Fresh attempts through bioinformatics efforts by two separate groups at the Venter Institute built alternative lists of genes. But the designed genomes from these two efforts again proved unviable and could not be resuscitated by additional strategies. At this point they went back to traditional genetics, and used transposon-mediated deletion analysis of each gene, to discover the set of essential genes required for viability. Through this process, they obtained a reduced gene set. But when they built this, it did not live.

At this stage they put back genes that they had left out, one by one, to test each additional gene for contribution to viability. This was a purely empirical effort. It was not a design process, this is trial and error, trying multiple hundreds. By this process, they arrived at one genome that was viable. This accidentally successful genome had 473 genes compared to the original 525 genes. Moreover, one-third of the 473 genes are without assigned biological functions in the available knowledge of microbial molecular biology.

The Venter Institute study misses the standards of a total synthesis project as practiced by scientists in significant ways. The parts and their relations remain unknown for at least 1/3rd of the genes in the viable genome. So if we compare the Venter institute's study to Khorana lab's achievement, we can see that the Venter study could not achieve reconciliation of the multiple perspectives. Firstly they lack a complete list of defined parts on each of the three perspectives: the minimal set and network of genes, the minimal set of cellular parts and pathways and the minimal physiological capacities of the cell. As a result, their project failed to get going on the reconciliation work typical of a total synthesis project. In sum, the contrast in the accomplishments of these two projects underscores that making a working system from scratch constitutes a distinctive kind of knowing, and making cannot substitute for explanations.

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Jane Calvert

Synthetic yeast: a tale of sixteen synthetic chromosomes

The aim of the synthetic yeast project is to redesign the genome of the yeast species *Saccharomyces cerevisiae*. The project is often referred to as Sc2.0. Several of the chromosomes have already been synthesised, and these results were published earlier in 2017 in *Science*, so some of you may already be familiar with it. There are two main reasons why it is relevant to our discussion today. First, it is the kind of project that people only take on thanks to the capacities for DNA synthesis. It reflects the kind of sentiment I heard expressed by the synthetic biologist Christ Voigt at the Synthetic Biology 7.0 conference: "Now that we have the ability to synthesise anything, what we do we build and what do we design with that capacity?" I am not necessarily endorsing his view that we can synthesize *anything*, but I am highlighting the kind of sense of possibility that DNA synthesis often inspires. The second reason I wanted to discuss this project is because of one of the questions which this workshop was organised around, one that resonated with me: 'what are the relations between organisms in receipt of synthesised DNA and those inheriting it from biological production or receiving it from another organism?'

The synthetic yeast project places itself in a trajectory with previous whole genome synthesis projects. These normally start with the polio virus in 2002. People usually then tell a story which goes through the J. Craig Venter Institute's work we heard about in the first talk. So in 2008 there was the *Mycoplasma genitalium* genome, which is one of the smallest known bacterial genomes, then there was the 2010 *Mycoplasma mycoides* work that Alok spoke about. Up to this stage the genomes had maybe included a few 'watermarks' but basically the genome sequences were the same as the wild type. With the 2016 paper we were introduced to a reduced genome, which was very different from the original sequence, so we began to see people using synthesis to change existing genome sequences. That same year there was also an attempt to systematically recode many of the codons in *E. coli*. The synthetic yeast project is an order of magnitude larger than previous bacterial genome projects. It also aspires to change the genome in many ways.

When the scientists first set out with the goal to design a new yeast, they could not easily decide what to do, because the number of possibilities was so large. What they decided to do was to design a yeast that could teach them biology.

In passing I should mention that some people see this as on a path towards the synthesis of the human genome, which I won't discuss myself, but Rob Smith will address this at the end of the day.

While this overview is the kind of history people usually recapitulate for the synthetic yeast project, others do go back further. One of the people on the project traces a history of synthesis back to the first synthetic gene in 1979, and then from there the first synthetic plasmid in 1990, allowing for a broader and bigger trajectory of the history of synthesis. By bringing this into my talk I want to point out that there are many different ways to think about the trajectories of synthetic genome projects, and that at least some members of the synthetic yeast project want to see themselves as part of a longer history than just synthetic biology narrowly understood.

Because yeast is the largest genome to be synthesized so far, it has been organised as a large international project with many different countries involved. The chromosomes are distributed around these different locations as we see here. The empirical work that I will draw on throughout my talk has involved spending time visiting these labs, attending their conferences, and interviewing the practitioners. I will discuss three things today. I will start with the synthetic yeast project as a whole, before moving on to specific discussion of the synthesis of some of the chromosomes

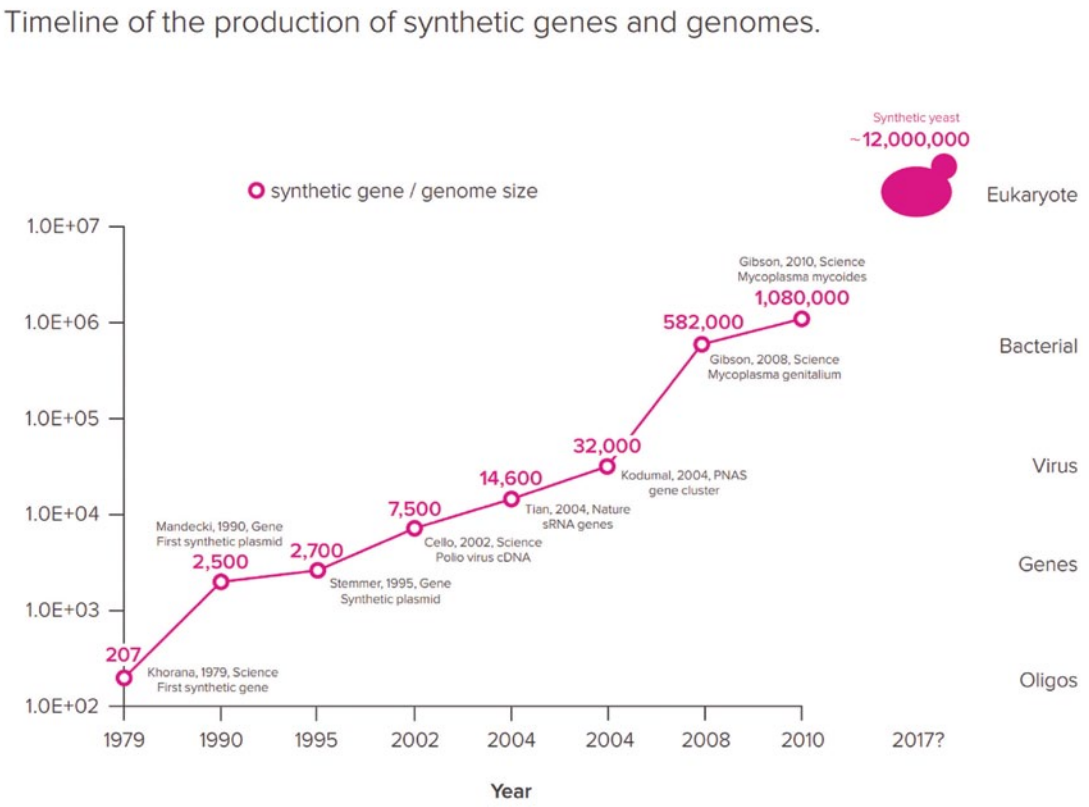

Fig. 4. Timeline of the production of synthetic genes and genomes, originally published in Sackler Forum 2015 *Trends in synthetic biology and gain of function and regulatory implications*. Reprinted with permission of Patrick Cai.

which have distinctive characteristics, and then finally arriving at the question of species identity and how this project may challenge it.

As a whole, the synthetic yeast project is often described as a 'refactoring' project, which is a term that comes from computer software engineering, meaning to rationalise and clean up software code. Synthetic biologists say they are doing the same to the genetic code. One of the earliest examples was the refactoring of bacteriophage from 2005. Refactoring is interestingly different from recombination, because it requires an overview of all the changes you want to make, it is not just about putting different bits of DNA into a recipient cell.

In addition to being a refactoring project, the synthetic yeast project is a design project. When the scientists first set out with the goal to design a new yeast, they could not easily decide what to do, because the number of possibilities was so large. What they decided to do was to design a yeast that could teach them biology.

They did this by adopting three design principles: (1) maintain the fitness of the yeast, (2) maintain genomic stability, (3) increase genetic flexibility. To achieve these aims they are making a range of changes to the genome, such as removing the introns, shortening the telomeres, and reducing the number of codons. The final synthetic yeast will be 8% shorter than the wild type. One of the most interesting design features, with the aim of increasing the flexibility of the yeast genome, is the so called 'SCRaMbLE' system. This enables large-scale genome rearrangements, including deletions, inversions, and duplications. It provides a new kind of experimental space for exploration, and also potentially leads to new yeast variants with industrial significance. This scramble system has been introduced across the whole genome.

The building process started out around 2007, when they began to order the DNA sequences that they needed from commercial companies. But they found this was taking too long and was prohibitively

expensive. So they decided to adopt a strategy of relying on undergraduate labour, introducing a course called 'Build a Genome' at Johns Hopkins University. The undergraduates were supplied with oligonucleotides produced by a synthesiser, which they then combined into 'building blocks'. The process has been a stepwise one of increasing scale, from so-called mini-chunks, to chunks, to mega-chunks. Mega-chunks are integrated into the yeast genome through homologous recombination, which is something that the yeast do naturally. It's a stepwise process where the synthesised DNA replaces the natural DNA sequentially.

The aim, as one of the scientists put it, was to 'create a living yeast cell whose DNA traces back to an oligo synthesiser, and before that to a computer programme rather than a parent cell'. This is very reminiscent of the Venter Institute's statements they released in 2010 stating that their synthetic *Mycoplasma* 'was the first cell to have a computer for a parent'. These examples matter for our discussion, because they show how evolutionary and genealogical relationships are cut, raising questions about provenance.

Having discussed the project as a whole, I will now discuss a couple of the individual chromosomes in more detail. I'll start with chromosome III, which was the first to be synthesised by Johns Hopkins and NYU in 2014. It was also the first yeast chromosome to be sequenced, in 1992. This draws attention to the fact that there are perhaps things we need to discuss about the parallel histories of sequencing and synthesis. Chromosome III is sometimes referred to as the 'sentimental favourite' of yeast geneticists, because it contains the genes responsible for sexual behaviour. It is also one of the shortest chromosomes, which was another reason for choosing to synthesise it first. Because it was the first chromosome to be synthesized, when they came to publish their work, the authors described the synthesis of the chromosome. This situation put pressure on authors of the future chromosome papers, who had to think of additional contexts and stories in which to situate their work.

There are perhaps things we need to discuss about the parallel histories of sequencing and synthesis

The next chromosome I will discuss is the 'neo-chromosome'. The reason for constructing this chromosome is to increase the stability of the genome overall. The scientists have taken the tRNAs, which are considered the most unstable parts of the genome, and they have put them all together in one chromosome. The downside is of course that you therefore have all the unstable elements in one place.

Because of this new chromosome, it might look as though the overall synthetic yeast will to have an additional chromosome. But this is not the case, because they are going to combine chromosome I and II. This will be done partially to keep the same number of chromosomes, and partially to increase the stability of the refactored and shortened chromosomes. At NYU they ran an experiment to see how many chromosomes could be combined, and found they could reduce the number of chromosomes substantially. This is a finding that might prompt questions regarding the identity of organisms and chromosome number, because chromosome number is one of the ways in which we commonly identify organisms.

In respect to species identity, I now want to talk about chromosome 12, which was synthesised at Tsinghua University. An important point here is that China is a very important country for the synthetic yeast project, with Tianjin University and BGI also involved. An interesting feature of chromosome 12 is that it has the 'barcode' for species identity. This barcode is used to identify *Saccharomyces cerevisiae*, which is a redundant and repetitive region in the wild type which we use in order to identify the species. But because it is redundant and repetitive the synthetic genome project has deleted it. Does this mean that the synthetic yeast is no longer the same species? This was a question that the scientists themselves raised. I see it as related to broader questions of species identity.

Lastly I will explain three of the chromosomes that have come late to the project, which are not particularly distinctive, but they raise questions for large genome synthesis projects. Macquarie University in Australia has two large chromosomes, and when I asked what was special or interesting about their chromosomes they did not identify any particular features. But what is interesting about their work is that they have a collaboration with the Australian Wine Research Institute. With AWRI they are building a 'pan-genome neo-chromosome'. They are taking the genes that are found in industrial strains, for instance the ones that are found in wine-making yeast, and putting them into a separate chromosome. This is not strictly part of the synthetic yeast project, but is something that they decided to do. This points to the kind of experimental space that is opened up by the project itself, and indeed a few of the other labs have also decided to create their own neo-chromosomes.

The final chromosome I will discuss is being synthesised by the National University of Singapore, the last group to join the project. This is chromosome XV, which is a very large chromosome. Here I want to draw attention to the fact that size matters and that building large chromosomes can be a laborious and mundane task. This contrasts with rhetoric in synthetic biology that sees design and construction becoming two separate spheres, with design requiring all the creativity, and construction being the boring bit, being taken over by machines in the future, or so it is hoped.

Group discussion

Marv. Has the neo-chromosome been synthesised already, and has it been made stable?

Jane. Yes they made it stable, it was a lot of work, not yet published. Required lots of knowledge of tRNAs, had to get flanking regions from different yeast species, it actually has 9 different species involved in the neo-chromosome in order to make it orthogonal to the rest of the system. They also are building it to have a different SCRaMbLE mechanism built in.

Marv. But when you put it into the total genome, with all the tRNAs are on that one chromosome, somehow one of those constructs has to figure out how to be stable in order for the cell to survive. But you won't know which one that is, just one of those neo-chromosomes will have to be stable.

Jane. There is an interesting project looking at the chromosome structure in 3D and how they fold. The image of the neo-chromosome in comparison to the other ones, it just looks like a tiny curled up thing. I do not know what that implies about how it will coexist with the others.

Marv. That leads me to ask, the one that works, i.e. that gets inside the cell, does it still have the same sequence as the one they made, or has it been recombined in a way that is surviving?

Jane. They do sequence it regularly to try and check, but I am not sure how long it takes for mutations or changes to happen. The publication of the papers in *Science*, in one of them they were keen to point out that it was a perfect copy of the design and came out exactly as it was meant to, but I do not know how long it stays like that.

Lijing. It seems that the two projects, Khorana and the synthetic yeast, are two modes of synthetic biology happening at different times, and are reflective of two different views at these times of how biology works. One way to synthesise a gene is to figure out each piece of the enzymatic process necessary, and through trial and error, asking new questions that build postdocs and people's careers over time. But in recent years we see a move to a more global conglomerate and large international collaborative approach, both to sequencing and synthetic biology. We also see this shift in 'big data' biology. How do the speakers see their cases fit into a larger historical context?

Jane. I agree that the parallel of sequencing and synthesis is very important. I think it also matters that some of the people involved in the synthetic yeast project like to connect themselves to the longer history of gene synthesis, where

other synthetic biologists might focus on a turn of the millenium context, and a renewed emphasis on the importance of engineering for biology. Venter has been doing the mycoplasma work for a very long time indeed.

Alok. The cell is very complicated. The number of tasks that it does is large. The fact that 17 chromosomes are being attempted across the globe, people are learning what it takes, and organising their project to find what it takes. I think the scale of project is matching the scale of the task structure. Also if we compare the two, the Venter project is working on something 1/6th the scale of the yeast genome.

Marv. This is not a synthesis story, but Spiegelman in the late 60s, I think it was bacteriophage R17, he put it under the pressure of time. He asked 'if I keep shortening the amount of time, what will happen?' And the answer is he was able to reduce the time it took to replicate that genome in the test tube from, I don't know what the numbers are, let's say an hour to five minutes. This organism learnt how to do it by shortening the chromosome and only putting the essential parts in, and the rest was discarded. Now in those days they could not sequence it properly so they had no idea what the sequence was.

Jane. Time is very interesting also in the Venter Institute's work, because they decided to move from the *Mycoplasma genitalium* to the *Mycoplasma mycoides* because the former was very slow growing.

Alok. Indeed the *genitalium* was slow growing to the extent that it did not have a defined doubling time. There is also a question of how much of the physiology we are able to map and play with. We do not understand the physiology that produces the doubling time, so this is not engineering in the hands of Venter because they do not know how doubling works. What is nice about the Spiegelman example is that you do not claim to know how doubling time shifts from an hour to five minutes. But if you let the cell replicate under pressure it will shuffle the mechanisms and make it happen, and you can come along and read out the sequence. But you are not designing or claiming to explicate.

Marv. Well I see design and synthesis going hand in hand. You go from synthesis to design, from synthesis to design, and you get to the end product of your process.

Roger. This to me is also how technology works. People try things and then see what works, change it, and see what works.

Jane. Synthetic biologists do talk about wanting control. They want to be able to design it and for it to work as intended.

Marv. Another question I had was to do with the labour involved. And the reliance on undergraduate labour. Well in industrial synthesis, even with the best chemistries, there is roughly 1 mutation every 500 nucleotides. So you have to put them together in blocks, then clone and sequence them in order to find the one that is right. That's where the labour comes in. Now, if you could improve the chemistry to bring this up to 1 mutation in every 2000 nucleotides, you might be able to get away with a lot less labour.

Dominic. I felt that in both papers there were always tensions about what to value at a given time. So in the first paper it was explained how so much of this was a chemical enterprise, but then to synthesis the gene they really had to rely on the biology. Could you both say more about these tensions? The times when labour is labour, and not that great, and times when labour is engineering and something more impressive. Or the times when a particular phenomena is worthy of attention or not worthy, because by alluding to it you might just actually expose your ignorance. Or the times when having an explanation seems to matter, and when it doesn't.

Jane. One of the heads of the synthetic yeast project is famous for some work on transposons, but in this genome they are getting rid of them. So in their case they once valued these components of a chromosome, but are now deleting them, which I think is a good example of something's value changing.

Marv. Do they know if they can delete all those transposons?

Jane. A lot of the deletions go wrong, and they find they have to put them back in again. Likewise with introns.

Marv. I would imagine that you're going to get a lot of people groaning very loudly when they realise that in order to use the synthetic yeast to explore a particular function, you're going to have to resynthesise x-number of chromosomes to recover the function you want to look at. Or the groans will come when they try and make the whole thing actually survive.

Alok. The question brought attention to differences between chemists and biologists, and the chemist recruiting the biology's unknown ability to complete the synthesis. The other tension here is between explaining and manipulating, and putting a technology in a box. Manipulation is a lot of fun, it gives you an enormous amount of novelty, but then there is bookkeeping to do for explanation.

Jeff. Something has changed to simplify these procedures to the degree that undergraduates or high school students can contribute to these international efforts.

Marv. High school students these days will usually be highly skilled when it comes to ligating and cloning. Having huge amounts of labour to achieve something in biology is not new. The first tRNA that was chemically synthesised with all the modified bases, that was done in China around 1978–81/2. They had literally a factory outside of Shanghai that did nothing but take natural tRNAs and fractionate them and isolate all the modified bases that went into a tRNA. A massive effort, 500, 1000 people? I don't know. Once they had enough of this material to put into a synthetic gene, they shipped it to the Shanghai Institute of Biochemistry and they then incorporated these modified bases into the right sites. So this was lots of labour too, it wasn't high school students but it was workers in a factory.

Jeff. So the ability to mechanise the process matters. But doesn't this require fundamental advances? If we look at Emil Fischer trying to synthesise proteins, he could never do it because he hasn't figured out the correct technique, so it wouldn't matter how many people he put on the job, he's not going to get there.

Session 2: Extending synthesis

L. Scott Cole

Selling DNA Synthesis: Applied Biosystems' DNA Synthesis Business from 1989–1992

This morning I'll be discussing the dissemination of automated DNA synthesis technology. That's what we did at a company called Applied Biosystems, or ABI, where I worked in the DNA synthesis group from about 1989 to 1992. Briefly, my background is in molecular biology. That's what I studied as an undergrad and in grad school, then I went to business school with the idea of working in the biotech industry. My first job was as product manager for the DNA synthesis business at ABI. I started there after the company had launched its first DNA synthesizer in 1983. So, for the earlier part of the brief history I'll be presenting today, I'll be relying on interviews I conducted recently with other ABI employees involved in DNA synthesis before me.

My presentation has three sections. First, I'll be talking about DNA synthesis platforms and technology. Second, I'll take an inward-looking view of the company, i.e. the people, processes and culture at ABI. Lastly, I'll take an outward view, i.e. focused on ABI's customers, applications, and competitors. I will present each with respect to two time periods: (1) 1983–87, which I call "market entry and development", and (2) 1988–1992, which I call "rapid market growth." The turning point corresponds with the commercial introduction of PCR technology, which drove growth in DNA synthesis. The reverse is also true: automated DNA synthesis enabled PCR technology to flourish.

What is a DNA synthesiser? Curt Becker, one of ABI's first employees called it a 'glori-

Fig. 5. *Clockwise from top,* (i) Andre Marion (*left*) and Sam Eletr; originally published in Springer, Mark (2006). 'Applied Biosystems: Celebrating 25 years of advancing science', *American Laboratory News*. (ii) Bill Efcavitch (*left*), Steve Lombardi, and Scott Cole (*right*); photograph courtesy of Scott Cole. (iii) Michael Hunkapiller; photograph courtesy of Scott Cole.

fied Coke machine' since it's fundamentally a liquid delivery system. A DNA synthesizer builds DNA strands ("oligonucleotides" or just "oligos") in disposable cartridges called "columns." A column contains a solid support matrix—basically, very small glass beads—upon which the oligos are synthesized base by base. The instrument performs successive cycles of chemistry. Every cycle adds a new base to the growing chain. At the end, the instrument performs a round of chemistry to cleave the synthesized oligos off the glass beads so they can be used in an experiment.

Automating DNA synthesis involved at least two challenges. First, the chemical bases in their precursor form, "phosphoramidites", are very expensive. This puts a premium on using very small amounts of chemicals in each synthesis cycle. Second, a few of the non-phosphoramidite reagents used in the synthesis cycle are toxic. A DNA synthesizer is designed to sit on a lab bench and not in an air flow hood, so the synthesis process has to be completely contained.

From a customer perspective, there are at least three important performance metrics. First, customers want very low reagent consumption. Again, this is because the phosphoramidites are so expensive. Second, they care about "coupling efficiency." This refers to the chemical efficiency of each base addition and determines the ultimate amount and quality of the oligo and the potential length of an oligo. Consider that if coupling efficiency is even 90% at each base addition, the 10% loss compounds with every base addition cycle and it becomes difficult to make even small oligos. Finally, customers care about "cycle time." How long does it take to make an oligo and therefore how many can I make in a day?

Let me provide some context regarding ABI. The company was founded in 1981 thanks to two complementary academic efforts: those of Marvin Caruthers' lab at University of Colorado, which focused on DNA synthesis chemistry, and of Lee Hood's lab at Caltech, which focused on automation. In fact, many of ABI's early employees came from these two labs, and also from Hewlett Packard, which was the largest instrument company in the Bay Area at the time. ABI's first product was a protein sequencer. The second was the DNA synthesiser.

Let me quickly give you a sense of ABI's early team and culture. The company had two founders: Sam Eletr and Andre Marion. Sam was a former H-P engineer: by all accounts very technically-oriented, competitive, demanding and even intimidating. But he was highly respected and really set the company's fairly aggressive, demanding culture. André was also an engineer. He worked with Sam at H-P and was the quieter of the two. A third key person early on was Mike Hunkapiller. Mike was a post-doc in Lee Hood's lab at Caltech and joined the company pretty soon after it was founded. Mike would eventually become ABI's president during much of the 90s and beyond. The fourth person I'll mention is Bill Efcavitch, a chemist from Dr. Caruthers' lab who was the head R&D person in the early years and beyond.

In short, the early team was engineering-focused and very competitive, with some strong personalities. ABI was not a "marketing-driven" company. Marketing as a corporate function was not highly respected. To be successful in marketing at ABI, really throughout the company's existence, you had to not only be able to keep up with the technical folks, you sometimes had to be capable of challenging them on technical matters.

ABI's culture and strong market position gave it a reputation in the market as being an arrogant company. A 2000 *New York Times* article about ABI said that in its customers' minds, "ABI" stood for "Arrogance Beyond Imagination." I more recently heard a story—so this is second hand—that when the protein sequencer, the company's first instrument, was launched, a salesperson would visit a potential customer lab and if that lab didn't place an order within three hours he or she would leave. Again, I can't vouch for that, but it wouldn't surprise me. Another quote from that same *New York Times* article was from the director of a large genome sequencing center (who was also a DNA synthesis customer) who said about ABI that, 'It's not that the customer is always right, the customer is always wrong'. These quotes highlight some negative aspects of ABI's culture, but that culture also made the company successful and made ABI an exciting, dynamic, passion-filled place to work.

What is a DNA synthesiser? Curt Becker, one of ABI's first employees called it a 'glorified Coke machine'

Sam and Andre's early vision was, in their words, to sell the picks and shovels to the miners in the biotech gold mine. The other pitch the founders made to early investors was that ABI was going to offer everything required for molecular biological research. That meant that for both proteins and DNA, ABI would develop platforms for both synthesis and sequencing. And it did. It launched these platform capabilities in the following order: protein sequencing, DNA synthesis, peptide synthesis, and DNA sequencing. The commercialization of these four types of platform delivered steady, rapid growth. As one platform would begin to plateau in the market, a new one would pop up and take its place, and so on. These successive roll-outs culminated with DNA sequencing, Celera Genomics and the sequencing of the human genome, which I probably won't have time to talk about.

But focusing again on DNA synthesis, the company launched its first DNA synthesizer, the 380A, in 1983. It was large and weighed a ton. It was a workhorse. It had three columns, so the user could make three oligos simultaneously. In 1983, many of the customers of DNA synthesizers were organic chemist "tinkerers." They weren't using the phosphoramidite chemistry that would eventually dominate the market, but a type of chemistry that was more "tinkerable." Many of these users had their own "recipes"—their own unique versions of DNA synthesis chemistry—that they wanted to implement on the instrument. The applications at the time that required synthetic oligos included studies of DNA-protein interactions and also reverse genetics. The latter required both a protein sequencer, which was ABI's first product, and a DNA synthesiser. If you could get the first bit of the sequence from a protein, you could create an oligonucleotide that

corresponded from a DNA code standpoint to its gene. The researcher could then use the oligo to find the gene and clone it. That was a way to use both of these instruments to do something that at the time was very novel and important.

Competition during this earlier period came mainly from Beckman, Biosearch, and Advanced ChemTech. Beckman had a tight relationship with Caltech. So it wasn't easy to establish a relationship with Caltech and get the licenses required to commercialize DNA synthesis technology. Most of ABI's intellectual property licenses were also made available to Beckman early on. [*From the audience:* Arnold Beckman was on the Caltech board]. That's right, and there's a Beckman building and Beckman everything down there. At the time, Sam Eletr made the argument to Caltech that large companies like Beckman with a lot of products wouldn't put that much effort into selling or developing Caltech's machines, whereas ABI was small and hungry and would focus on it much more. And probably that ended up being true.

When the 380A launched, the competing instruments were smaller and less expensive than the 380A, and in some ways were more flexible. By comparison the 380A was like a Mercedes: big, solid, heavy and expensive. One aspect of the 380A and other ABI instruments that we always emphasized was their "valve blocks." These valve blocks replaced the flexible tubes that transported liquids on competing instruments. They were developed at Caltech and were unique to our instruments. They resulted in very low liquid volume waste, less mixing, and better cleaning between cycles. We would always claim that we had the most precise, frugal liquid handling technology on the market.

But, again, those other instruments were much less expensive, and some labs just didn't have the money for a 380A or, later, the very similar 380B. So, in 1985 ABI launched a smaller synthesizer called the 381. It had one column and was much less expensive. The idea was to stop Pharmacia in the places they were strong, namely Europe and Japan, and to fight the company that by then was called Milligen Biosearch in the US. Their Cyclone was really a pretty good DNA synthesizer.

In 1983, many of the customers of DNA synthesizers were organic chemist "tinkerers." They weren't using the phosphoramidite chemistry that would eventually dominate the market, but a type of chemistry that was more "tinkerable."

Then, in 1985 the market changed with the introduction of a technique called PCR, which is essentially a way to make very large quantities of any relatively small stretch DNA. Think of a photocopier. PCR was important to our business because any time a researcher wanted to do PCR they needed to make two small oligos of unique sequence. So, labs were now constantly needing small oligos. PCR was invented in 1983, presented at a conference in 1985, in 1987 it was starting to become commercially available. Then it absolutely took off and this was a game changer for DNA synthesis. Again, the relationship between PCR and DNA synthesis was synergistic. PCR drove DNA synthesis sales. But DNA synthesis was required for PCR technology to spread as fast as it did.

To take advantage of the PCR opportunity, in 1989 we launched the 391 PCR-MATE. This was basically a 381 that was rebranded, updated with a more modern user interface, and cost-reduced a bit. We also sold it as "user-installable" for about $3,000 less than the same instrument installed by an ABI service technician. We did this to better compete with our lower priced competitors. Really, though, the 391 was never installed by a user because no salesperson wanted to risk having a customer mess up the install. So, the 391 was pretty reasonably priced if you bought it as user-installable and then took advantage of your salesperson's offer to help!

The 391 helped us ride the PCR wave. Then, in 1991, we launched what became the very popular 392 and 394 instruments. These were basically one and the same instrument outfitted with either 2 or 4 col-

Fig. 6. *Left*, a photograph of a 380B model, launched in 1985. It looks very similar to the 380A; image courtesy of Scott Cole. *Right*, Bill Efcavitch overseeing the installation of the 380A in the Caruthers lab, 1983; photograph courtesy of Marvin H. Caruthers.

umns, and either 5 or 8 phosphoramidite positions. And everything was upgradable after purchase. In other words, if the customer only had enough money for a 392, they knew that when they got more grant money they could upgrade their instrument to 4 columns. And, just as important, both the 392 and 394 finally had columns in multiples of two, which makes sense for PCR since a PCR amplification always requires two oligos. This was constantly a sales issues with the 391 versus its mostly 2-column competitors: "You call it the 'PCR MATE' but it only has one column!"

By the late 1980s, oligos for PCR represented about 90% of the demand. And by this time typical DNA synthesizer customers were no longer organic chemist tinkerers. Customers were now molecular biologists. ABI had become far and away the market leader because of their instruments' performance and reliability but they were expensive for an individual lab. So, departments started setting up what became known as "core labs." These were centralized facilities managed by a small staff. They enabled shared purchase and shared use of expensive instrumentation among several or many labs in a department.

In the early 90s, competition was still coming from some of the same companies I mentioned earlier. But now there were also competitors that only offered DNA synthesis reagents. Companies wanted to take away our reagents business, and some of the companies were offering high quality reagents. ABI always had a policy that if customers used non-ABI reagents, they would void their instrument warranty. Customers didn't like this. It was the epitome of 'Arrogance Beyond Imagination'. But it helped us maintain most of our reagent business. Our other selling point around that time was our "whole product" approach. ABI emphasized that in addition to instrument and reagents, a DNA synthesis supplier had to provide strong service and support. Given our market dominance, we had the largest and best service and support organization by a long shot. Customer conservatism also helped us. Customers felt safe going with the market leader. There's an old saying: "Nobody ever got fired for buying an IBM mainframe computer." The same was said about ABI.

Now for a quick internal perspective. During the time I've been talking about, processes within the company remained pretty flexible. If a product manager had to get around things or do something quickly, he or she could. And the technical knowledge within the company was unrivalled. The main Foster City (California) campus housed employees who knew an enormous amount about the various technologies relevant to DNA synthesis and who knew how to design, develop and manufacture very high quality instruments and reagents. Being near Silicon Valley, ABI had access to a lot of experienced engineers and scientists. And globally we typically

had more than 80% market share. That meant we had the most salespeople talking to the most customers. Tech companies often get the best new product ideas from customers. Up to a point, success creates more success.

After 1992, commercial oligo services began to take off. Researchers stopped buying as many synthesisers and instead ordered them through the mail. And, around this time, ABI started focussing more on DNA sequencing. As I said before, sales of a new instrument platform can grow very quickly for several or more years, but eventually start to plateau. That's when it's important to launch a new kind of instrument that has greater growth potential. So, the objective at this time was mainly to protect our DNA synthesiser business. We did this by continuing to innovate: offering smaller columns for less expensive synthesis on the 392 and 394 and also by releasing of a much higher throughput instrument: the 3948. There was also growing interest in other applications, such as large-scale RNA synthesis for pharmaceutical applications, at least their research divisions.

Our other selling point around that time was our "whole product" approach. ABI emphasized that in addition to instrument and reagents, a DNA synthesis supplier had to provide strong service and support

Time is up, so I'll conclude by quickly emphasizing a few the points I made earlier. First, I want to emphasize the importance of the culture and community in the success of ABI's DNA synthesis business. Second, I hopefully conveyed the degree to which commercializing a platform like an automated DNA synthesizer requires a highly multi-disciplinary scientific and engineering team. Finally, history shows how various research technologies are interlinked, both technically and in the market. Recall the synergy between ABI's protein sequencer and DNA synthesizer in early reverse genetics applications as well as the mutual dependence of DNA synthesis and PCR for each of their proliferation and success.

Marvin H. Caruthers

The Chemical Synthesis of DNA, RNA, and Certain Analogs

I am intending to give you some more of the history of DNA synthesis, to give you some stories and go from there. I would like to start with a quote from Frederick Sanger, where he is discussing his work on DNA sequencing. "Most of the significant work has been summarized in a number of reviews and articles. In these there was, of necessity, a good deal of simplification and omission of detail, both for reasons of space and, sometimes, to make a good and logical story. With the passage of time even I find myself accepting such simplified accounts"—I too will be giving you a simplified overview of several topics along the way, through the history of DNA synthesis.

In 2005 I had the honour at the 50th anniversary of the first synthesis of a dinucleotide in Cambridge, of presenting the introductory talk, which I gave as a history of DNA synthesis. So I have a whole lecture of slides on this topic, and I started with Lord Todd. It was published in the *Journal of the Chemical Society.* Todd was best known because he determined that DNA and RNA were made of ribose and deoxyribose sugars, and the linkages were phosphate 3–5, sugars were linked to the nucleoside bases, and he defined the structures of all these components, the bases included. This was mainly in the 1940s but some of the work in the 1930s, and was the main focus of his Nobel prize. When he completed the synthesis in 1955, in his Nobel lecture two years later, he states "synthesis can serve not only in the elucidation of structure, but can in many instances open up wider vistas regarding the significance and function of biologically important compounds". In other words, unlike most organic chemists, at least 99% of them, who were using synthesis just to attack organic synthesis problems, such as a 20 or 30 step proposal

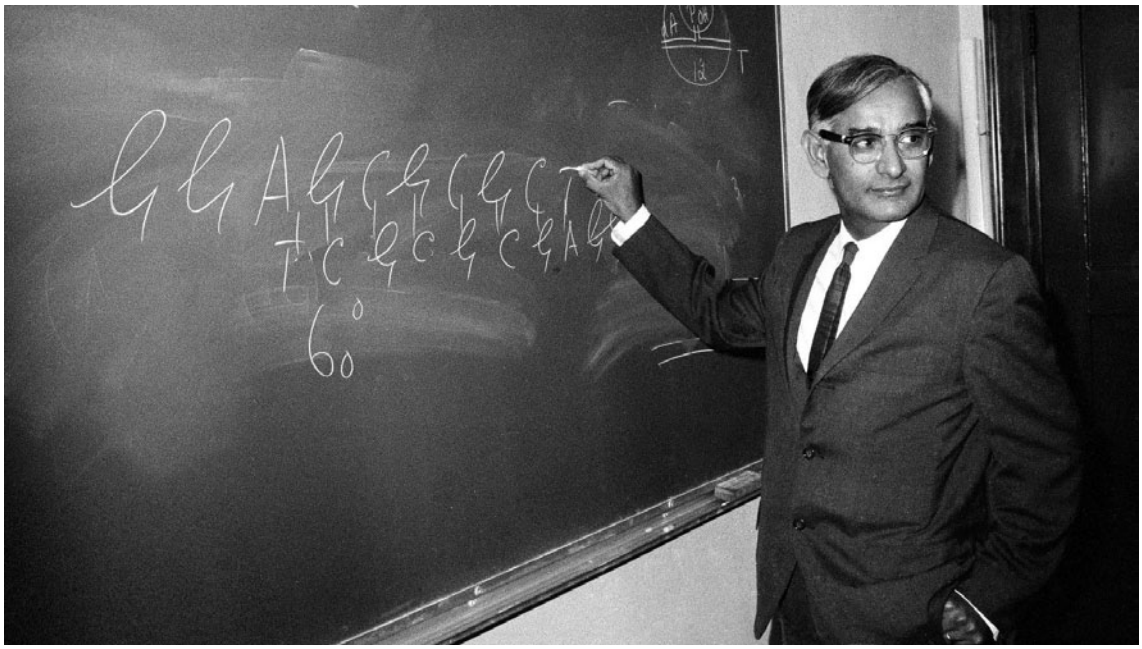

Fig. 7. Har Gobind Khorana in 1970. Associated Press, file 700602089.

to synthesise some natural product, and once it was synthesised move onto the next one, rather Todd's focus was building these new molecules with a focus on biologically important compounds that could be used to attack biology. He was saying this as early as 1955, long before the concept of bioorganic chemistry which became popular in the 1980s and 90s.

Then Khorana came along. He got his PhD with George Kenner in Liverpool, moved to do a postdoc in Prelog's laboratory at the ETH in Switzerland, and then moved to Cambridge to work in Todd's group, where he developed the methodologies for forming pyrophosphates and synthesising ATP and coenzyme A. And then he moved onto the problem of synthesising oligonucleotides. The first major involvement with them was using repeating trimers, and tetramers, and dimers, to help elucidate the genetic code, and for that he shared the Nobel prize with Marshall Nirenberg. Later on, I myself got into the Khorana lab in the late 1960s, and the project that was under way at that time was trying to synthesise a gene. At the time we started this project in 1965 there was only one specific RNA sequence that had been carried through and that was Bob Holley's work on yeast tRNA alanine. So Gobind set up the lab and started to synthesise the gene for this particular transfer RNA, with the sequence that came out of Holley's lab. Why did he want to do this?

The following quotation comes from a jubilee lecture in 1968, 'why would anyone want to synthesise a gene?' His objective was to develop methods where you could precisely define the sequence of DNA that you put into a piece of synthetic DNA. He says: "We would like to know, for example, what the initiation and termination signals for RNA polymerase are, what kind of sequences are recognized by repressors, by host modification and host restrictive enzymes and by enzymes involved in genetic recombination and so on." He goes on, " the next long-range aim must be the development of methods for the total synthesis of biologically specific DNA duplexes". He was using the synthesis of this gene as a template to develop the technologies to define sequences of DNA. This was the purpose of this work.

It is worth commenting how much work it took to chemically synthesise a 20mer at this time. For instance, one part of the duplex for this part of the tRNA gene was synthesised by Hans Weber, and it was a two year project. It took him two years to make that 20mer in the mid to late 1960s.

All the assemblies of the gene were accomplished by synthesis plus ligation, ar-

riving at the final product of the 77 piece duplex DNA. But the point is that this was a template for developing methods for sequence defined synthesis of DNA. We felt it was quite an achievement successfully putting together a 77 base pair duplex. We then published the 13 papers corresponding to this total synthesis as one complete issue of the *Journal of Molecular Biology* which came out in December of 1970. Subsequently a commentary that came out in *Nature*, from a cell biology correspondent, states "the thirteen articles from Horana's group which comprise a complete issue of the *Journal of Molecular Biology* surely set something of a record....Every step of this synthesis has obviously been executed with consummate skill and the whole constitutes perhaps the greatest *tour de force* organic and biochemists have yet achieved." I think I would agree with that, and Gobind's whole view was on the very horizon of what you can do, so everything you do there is a *tour de force*, it is never done simply. But then here comes the zinger: "Like NASA with its Apollo programme, Khorana's group has shown it can be done, and both feats may well never be repeated". Many times when I am presenting in England, if I know there is a *Nature* editor in the room, I try and bring this slide up.

I also want to add a quote from a paper that Khorana gave in 1968: "I wish to conclude by hazarding the following rather long-range predictions. In the years ahead, genes are going to be synthesized. The next steps would be to learn to manipulate the information content of genes and to learn to insert them into and delete them from the genetic systems. When, in the distant future, all this comes to pass, the temptation to change our biology will be very strong." That was 1968, at an international biochemistry meeting in Japan, he had this as part of his talk. Of course we are already doing that with yeast and several other organisms.

The point here is that we could not express that tRNA gene biologically. So in 1968 we started work on the synthesis of Tyrosine Suppressor tRNA. The idea this time was to synthesise a gene that we could express and look at its biological activity. Here we looked at lambda phage virulence. There is a story here I want to tell you about. We sat down in one afternoon in 1969 I think, to lay out the synthesis of this structural gene. We spent 2 or 3 hours doing this because Gobind had a history of going to La Jolla in January, there was a small group that Francis Crick put together where they would come and talk about their research every year, and Gobind wanted to present the plan for synthesising this gene at that meeting. After spending a few hours talking about how to synthesise it, we turned to the discussion of how we were going to express this gene. Well at that time we didn't know anything about promoters, or terminators, how to get this gene into a cell, or anything like that. So we sat around and talked about it for a while. The only clue we had to go on, was that Ray Wu at Cornell had just sequenced, by a very difficult methodology, the sticky ends of phage lambda. We kind of thought 'maybe there is some way we can attach this to the sticky ends of lambda and try to transfect it, sit down on our knees and hope and pray that something would come out of that'. We had no way of knowing how to incorporate this synthetic gene into a bacterium and have it be expressed. So Gobind was listening to all this, and this is what is important, after about 25–30 minutes had gone by he stood up - in other words the meeting was over - and he said 'well let's synthesise the gene first, and by the time we get it synthesised we will know how to express it'. In other words, science is going to move far enough along that we will know how to express it, and that is the way that Gobind did his science.

Our lab has the honour of being one of the first two labs to show that synthetic DNA has biological function. Both my lab in Boulder and Arthur Riggs in collaboration with Saran Narang, had synthesised the lac operator sequence, both by different methodologies but we got the same sequence

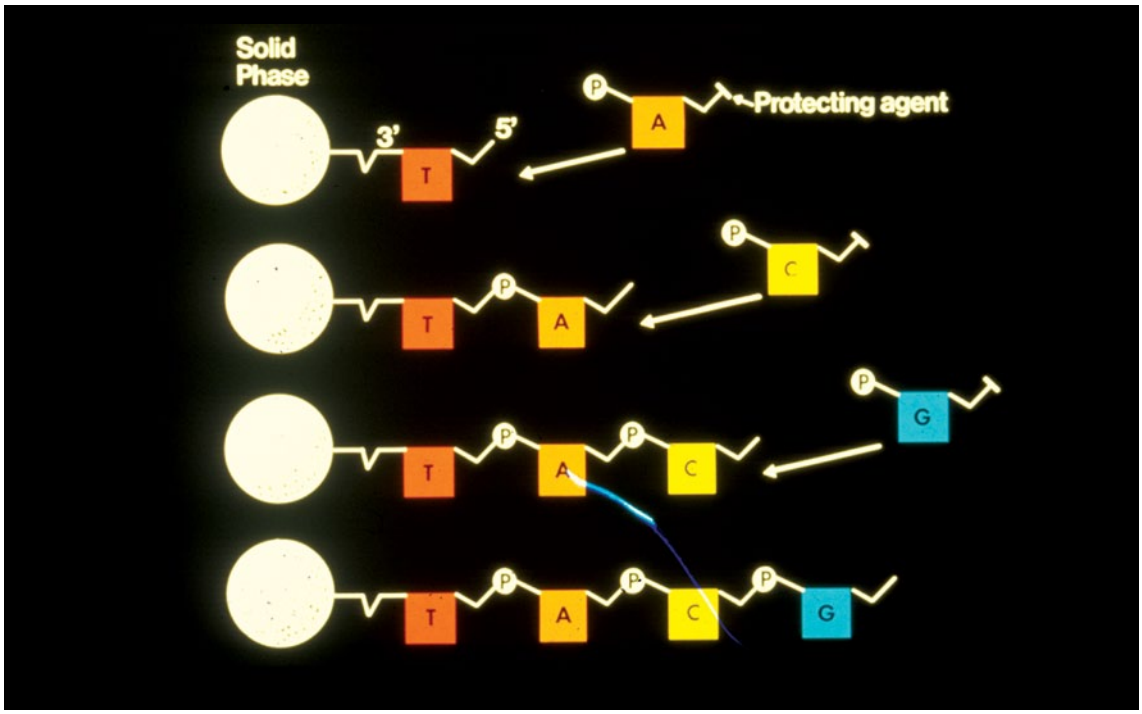

Fig. 8. Slide depicting the process of synthesising DNA through the solid phase approach. Image courtesy of Marvin H. Caruthers.

After Gobind's death in 2011, myself and Robert Wells in our retrospective, we wrote: "Gobind was a dedicated, driven, focused, and humble scientist. He was fiercely loyal to all whom he mentored and worked with, and unyielding in his drive toward the highest scientific ideals and goals. He repeatedly attacked immense and challenging problems, likely with little idea of how he would eventually solve them—but solve them he did." That was Khorana.

I was fortunate that I worked with Bob Letsinger as a graduate student. When I spoke to him, as you're interviewing for places to pursue your work, he was trying to develop methods for synthesising macromolecules on polymer supports, and I thought that was really a neat idea because nobody had ever tried that before. I specifically chose North Western to work with Bob, and so as soon as I arrived I began working in his lab. At that time he had a postdoc in his lab, Milt Kornet, who had just synthesised a dipeptide on a polystyrene support, and we were pretty excited about that. A month or so later, Merrifield published his Tetrapeptide synthesis in *JACS* also on polymer support, and the two labs didn't know that the other was working in that area. Bob and Milt wrote up their work and published it all the same year in *JACS* as Bruce Merrifield's work. Unfortunately Bob did not share that Nobel prize, it was given entirely to Merrifield. But Bob turned his attention to DNA synthesis and figured out a new method for making DNA, again on a polymer support. Myself and a number of other researchers in the lab worked on other methods for synthesising on a polymer support as well, and all this came down in the middle to late 1960s. Here I quote from a short article I wrote about Bob: "Over the years, as I observed how others direct their programs, I consider myself one of the most fortunate of graduate students. Somehow, I found a mentor who was patient, who allowed students to explore their potential, and who focused his research on extremely challenging problems." That was Bob.

We went ahead, and our lab has the honour of being one of the first two labs to show that synthetic DNA has biological function. Both my lab in Boulder and Arthur Riggs in collaboration with Saran Narang, had synthesised the lac operator sequence, both by different methodologies but we got

the same sequence. And then in collaboration with Jack Sadler down in the medical school in Colorado, and Saran in collaboration with Art Riggs at City of Hope, we independently cloned this operator into *E. coli* and got expression. This was presented at the Cold Spring Harbour Symposium in 1976. Their group published in *Nature*, and we held off until 1977 to publish in the first issue of the new journal *Gene*. This was the first piece of synthetic DNA that showed biological activity that had ever been published. From there using the chemistries that Bob Letsinger pioneered various labs started synthesising biologically interesting DNAs. Shortly thereafter, Genentech in collaboration with Art Riggs at City of Hope, published the synthesis and cloning of human insulin, so both the synthesis and the biological activity. By that time two graduate students from my lab had gone on to become two of the first four employees at Genentech, Dave Goeddel and Dan Yansura, both of whom were part of the expression team.

My lab got involved in solid-phase chemical synthesis around 1976 or thereabouts. In those days we were very much involved in protein - DNA recognition. But I had a new graduate student, Mark Matteucci, who wanted to do a project more on organic chemistry. So I suggested we try and develop a methodology for synthesising DNA on supports. Mark picked up this challenge and was focussed on using control pore glass and adding nucleotides one at a time, and then in collaboration with Serge Beaucage who developed as a postdoc the phosphoramidite synthans, we developed this chemistry for synthesising DNA. This is perhaps where I should stop, but I had wanted to explain how I got involved in applied molecular genetics and from there into Applied Biosystems, but I have run out of time.

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Group discussion

Dominic. It seems there is a wide variety of ways to synthesise DNA, and it can be hard to understand the differences between them. Are there ways you could characterise what makes different chemical approaches distinctive?

Marv. Well to be honest they're all pretty archaic so I wouldn't worry about it.

Dominic. But historians think archaic things are pretty cool!

Anonymous 1. I also would push back on the question, because everyone is using the phosphoramidite chemistry, the only difference is what is the hardware to build those oligos.

Lijing. What was considered the significance of tackling tour de force questions in biology, and how was this kind of activity rewarded in biology?

Marv. I have to tell you that molecular biologists, biochemists, were not sitting around eagerly waiting for someone to develop methodologies for DNA synthesis. They couldn't care less in those days. They weren't interested. For example the first Gordon conference I went to in 1975, by that time I had worked in Khorana's lab, Letsinger's lab, and so I was given the responsibility of reviewing DNA synthesis at that time. And so I did. Then that night I was sitting around a table having a beer and one of the individuals who was attending that conference, he said "Marv, why do you want to learn how to synthesise DNA? There's no reason for it. Sure, Khorana used it to solve the genetic code and now he's made his gene. So what else are you going to do with it? Why are you wasting your time learning how to synthesise DNA. You're a bright guy why don't you do something more interesting?" That was the mentality. He was not alone. You go out

in the world and apart from the aficionados who were working on DNA chemistry and struggling to figure out a way to make it, and in those days we had not even started on the phosphoramidite method yet. There was no interest in DNA chemistry at all to speak of, even though Khorana was out there preaching how, 'once we can make DNA of a defined sequence we're going to be able to do all of these other applications'. But nobody was really listening to him.

Roger. What did you say to him when he asked?

Marv. We had started out research in Colorado trying to understand how the lac repressor interacts with lac operator, and lambda phage's C1 repressor and Cro repressors interact with their binding sites on phage lambda. So we were making these DNAs synthetically using the old chemistries. So we already knew that there were certain applications that you could direct your chemistry towards once you had it developed in biology. There were a few of us around like that, for example Sanger in collaboration with a former postdoctoral student from Khorana's lab had synthesised at Cambridge a 12mer that they were using for priming sequencing work on φX174. This was the precursor to all the DNA sequencing techniques that we use today. So they were using primers in 1975–76 to develop what they called and presented at the '77 Gordon conference 'plus minus sequencing for DNA.' They were doing that with DNA primers. So if you go and look in the right places there were laboratories that were starting to use synthetic DNA to attack important problems. Not a lot but there were some. And if you looked at Khorana's paper you understood why he was doing this. As I showed in that quote, there were a large number of biological problems that required synthetic DNA to attack them. But the biological community, they just weren't interested in those days. Unless you teach them something, doesn't matter if it's sequencing or synthesis or whatever, once they are taught this they say 'oh yeah that was obvious of course we are going to use it'. Until you make it available it's like "why are you doing this?"

Alok. The beginning of the solid-phase synthesis chemistry, is what was being called the 'hardware'. This hardware though, might be more seen as a platform for integrative buildup. Because the hardware story is about 96 well plates, beads don't give us the next performance curve and so on. So the platform unlocked a new regime of yield, scale, and variety. Is assembling the platform another example of tour de force kinds of project?

Anonymous 1. I think you are getting onto something. When you are thinking of making a synthetic gene. Building your oligos is only one part of the project. You then need to assemble them, fishing out the errors. only 1 in 1000 base pairs going wrong is pretty good but it's not perfect. so you still have to clone and pick the perfect ones. To do that and scale up to 100,000s, you need to automate everything.

Marv. When we first got this chemistry going, all biochemists, biologists, molecular biologists used it. They were 'oh wow we can make 20mers'. And they were very happy with that for at least ten years. Honestly it was a few people who started going around to, not so much Applied Bio, but other companies asking 'can you make 100mers because we have some projects that require 100mers?' Then maybe even larger, 300mers etc. It was actually these people coming and asking for larger compounds. And they were driving things along, wanting larger compounds meant we needed better yields, driving chemistry and instrumentation forward.

Anonymous 1. And this has an effect on price. In 2000 a fully made gene would cost $20 a base, now it's 9 cents a base. Wait a few more years and it will be 2 cents a base.

Marv. And people didn't realise what you could do with larger DNAs until you could give them access to it.

Alok. Can I make a comparative point then? The organism genome platform which the Venter Institute is developing, which the yeast SC 2.0 Cre-lox system, is a wet-ware equivalent to hardware?

Marv. This is what we're saying. It's the development of the ability to make longer sequences that is leading to the current revolution in what you can do with them.

Jane. Everyone touched on sequencing as well as synthesis, could you say more about how they are related?

Marv. The current methods of sequencing require synthetic DNA. And that was the way it was for Sanger's first method. You need synthetic DNA to sequence DNA.

Anonymous 1. One pushes the other. It's as with any human endeavour. If you can read, that's good. If you can write, that's good. If you can do both then that's great. At the moment I think synthesis is a little bit behind, and we need to catch up the writing to the reading.

Scott. To go back to the era I was talking about, I described how PCR drove the DNA synthesis business, and DNA synthesis drove the ability to do PCR. Ultimately what made ABI's automated sequencer, which was the dominant sequencer at the time, was the use of a cycling method in the chemistry. So you can draw a path from synthesis to PCR, PCR people start thinking in terms of cycling, and going to a cycling version of the chemistry that made DNA sequencing robust.

Dominic. At ABI you mentioned there were quite a lot of engineers working there, and I was wondering how much biology they would end up having to learn? And could you say more about the relationship between ABI, the Bay area, and universities?

Scott. This is true for DNA synthesis, but even more so for DNA sequencing. DNA sequencing, for example, requires marrying expertise in chemistry, fluorescent dyes, molecular biology, optics, gel matrices, firmware and software. You have an organisation of people who are good at their own discipline, and who are also learning how to interact with other scientist and engineers whose parts of the platform touch their own. Engineers don't become experts in chemistry, for example, but everyone has to be conversant and reasonably knowledgeable in multiple domains, and that just comes through interaction with co-workers. As an organisation the ability to develop products in a multidisciplinary way becomes a source of competitive advantage. A company like ABI becomes very skilled over time at integrating very different technologies to achieve a goal.

You asked about the Bay area. ABI had a lot of relationships with folks at Cetus and then Roche. It's complicated, but Perkin-Elmer who had the market for PCR, bought ABI, so when that happened ABI also had PCR, at least for the research market.

The universities in the Bay area for some reason we never seemed to get along with. I don't know why. We had reasonable relationships with Berkeley and LBL, but other than that, we didn't. Relationships with several non-Bay area universities and organisations ended up being important, though. Thinking now of DNA sequencing, not DNA synthesis, the key relationship we had was with TIGR (The Institute for Genomic Research) and TIGR's founder, Craig Venter. He had the attitude that he was going to work with us and not try to beat us. Most of the genome sequencing centres wanted to develop technology to avoid buying from us. Craig's attitude seemed to be "My competitors don't like you so I'm going to be your best friend. You supply the technology and we'll focus on what we're good at." That, I think, was smart. Because of their attitude and approach to us, TIGR was always an early test site, they would get insights into technologies in development, and they got other kinds of preferential treatment.

Being close to Silicon Valley was really important, and that classic H-P culture and attitude, embodied in Sam Eletr, Andre Marion and a few other very early engineers, was the basis for ABI's early culture.

Marv. It's worth commenting that what really drove the development of modern molecular biology and biotechnology was the fact that in the mid to late 70s the technologies for DNA sequencing, DNA synthesis, recombinant DNA technologies, cloning, restriction enzyme modification, they all came down within a 3,4,5 year period. All of them. And that revolutionised biology research undoubtedly. And they all came together at the same time. If any one of them had come up by itself, and then only 15 years later another one came along, it's a whole different story. We wouldn't

be sitting here talking about what we're talking about. But they all came together at the same time and all at once the world exploded with new ways of attacking serious and important biological problems. What we're talking about in terms of DNA synthesisers and protein sequencers and so on, this is all part of that movement, because all at once people needed these compounds, products, and technology to do new state of the art biology. So they were pushing the development of these techniques.

A story that you don't know about Applied Bio, we actually started that company, Lee Hood and I, with these venture capitalists as an outgrowth of the group that started Amgen. We decided to go forward with starting Applied Bio, and we hired Sam Eletr. The point is that what Sam did, these machines the DNA synthesiser and protein sequencer, were in such high demand that he went out and he acquired contracts from 20 individuals or labs or companies, 20 on the DNA synthesiser and 20 on the protein sequencer and told these people 'OK if you want to be in the queue, you're going to have to pay half the price of what we're going to offer these on the market. We haven't designed them yet, and we certainly haven't manufactured them yet. But just to get in the queue you're going to have to put down 50% of the selling price'. And with that he built the company. There was so much demand in those days for these machines that he could do that.

Roger. I was wondering more about customer bases, and a broader historical question about science funding and changes that happened in this revolutionary time in the late 70s to early 80s. Who is buying most of these products, is it mostly universities, or private companies, pharmaceutical companies that have their own research institutions?

Marv. All of the above.

Roger. But who was the bulk?

Scott. There was no bulk. Industrial, pharma stuff, biotech, academic, medical centres.

Marv. And the manufacturer of the machines could not keep up with the demand. It was that simple.

Dominic. Would you say different things to the different customers when you were visiting them?

Scott. Not generally. This is an industrial sale. Platforms have specifications. You're comparing your product's performance to your competitors'. It always seemed like there is a striking amount of animosity between companies in the instrumentation industry. This is probably because potential customers have set budgets, every company knows when a given lab intends to purchase a DNA synthesiser, the same three companies and sales reps will be invited in to make their pitch. One will win everything. The others come away with nothing. But every customer wanted high quality DNA, cheap and fast. So there were similar sales points to be made with most customers.

Dominic. Would you be able to create an example for us, to do with the kinds of thing they may say about you, and you about them?

Scott. Oh, we would show gel data of our very clean oligos. They would argue our valve blocks weren't as good or as important as we said they were. They would blow out of proportion any reagent problem that we might have experienced recently, and we would do the same. We'd talk about competing instruments' lack of reliability. Fear is an important motivator, especially if you're the market leader. You want to create doubt. You don't say it directly, but it's understood that if you, the customer, buy a competitor's instrument for $20,000 less you're taking an almost personal risk that it might not perform. An instrument purchase is a highly visible decision within a department. So those kinds of arguments played a role. But most sales situation involved technical debates about issues that to outsiders would seem like pretty modest differences.

Marv. Before Scott's involvement at ABI, they had the market for DNA synthesis for five or so years, almost entirely exclusively. Pretty much in protein sequencing too. So they built up a client basis which was basically everybody in the industry, and then the Biosearches of the world and Milligens came along.

Scott. Even when I was there we always had roughly 80% of the market share.

Marv. I mean, when we started Applied Bio I was pretty upset that we had to cross-license our patents to Beckman. And Sam said 'Oh don't worry about it, we'll be on the market and have 80% at least before Beckman gets their first prototype built'. And of course that's the way it was. Because we were a small startup, we weren't a big monolith of a company called Beckman instruments.

Session 3: Objects and epistemics of synthesis

Erin McLeary, Stephanie Lampkin, and Amanda Mahoney

The material heritage of DNA synthesis?

We saw this workshop as a great opportunity to think about, say, if we were to build a museum to showcase this history what would we collect? What artefacts, what stories would we collect, who would we be telling them for? We want to work through these questions with the group.

For instance, if GE were to offer us an ÄKTA Oligopilot for free for our imaginary museum, why might we want to collect it?

Scott. Is it an early DNA synthesiser? It's actually a pretty recent one, and I think it's an *affordable* synthesiser for non-specialist labs. But if it is not immediately familiar to people, is it the kind of object the museum would want to collect? What about then something like reagent bottles, which everyone can recognise? Would we want to make space in our museum facility to take care of these, and would we want the actual chemicals?

Going back to the oligopilot—how do we think it would look in an exhibition? Not everyone is particularly interested in the history of DNA synthesis. What would we need to tell a history of it?

Scott. But I don't know how it fits into that story, so I guess I want to know what the story is. I'm wondering why it came from GE, I'm curious.

This instrument came into our presentation simply because I googled 'DNA synthesis instrumentation' and this was the smallest instrument I could see, I did not want to pick a large one. It also was not mentioned in any of the studies I have read, it wasn't cited as being used, so I chose it as an odd example. It helps illustrate the kinds of choices that museums have to make.

So one story we might want to tell, would be to take the reagent bottles, and the more recent machine, and perhaps tell a history of automation.

Alok. GE acquired a company a few years ago called Amersham, Amersham had the AKTA HPLC system, which got extended to compete with ABI to produce their synthesiser. So there is a certain history of taking a platform and growing it into an application that has generated its own market. So we could see this in a museum as an example of how technologies get combined.

That's a great comment first because it brings in a corporate history that most people would know nothing about.

Alok. Those knobs and that stack of boxes is well known to people.

Because it's HPLC?

Alok. Yes.

So how would we preserve this history?

Alok. Well I would maybe walk along Amersham's HPLC line and then show "well the next thing they did was…"

Dominic. And you could trace it back to some of the first synthesis machines because reworked HPLCs were used widely.

Certainly our museum has a number of HLPCs so we could tell that story.

Marv. Maybe if you contact Applied Biosciences and see if you could get hold of one of their first. Then you could find someone who was working in a smaller lab who couldn't afford it, and get one of their systems that was not really designed as such but was being used to synthesis DNA. After that you might have a bunch of arrows going to the applica-

tions of DNA, such as PCR, and sequencing, you might want to show a sequencer or a little PCR thermocycler, something like that. You would then have a little story where you start with manual DNA synthesis, then going through the Applied Bio machine and then these applications that come out of it.

So you're thinking about sourcing, how to find these instruments.

Jeff. A couple of years ago I was at the Deutsche Museum in Munich and they have a really big collection of these early devices. Subsequent to that I went to London and they only had one thing on display.

Anonymous 1. One way to make it less boring would be to show those four bottles, blue, yellow, pink, and green, those are ACTG, through the tube at the end comes a long letter of DNA. Putting things together on a machine.

So you're connecting this kind of grey box with DNA, which is something most people who know a little about science will understand. Another thing to notice here is that this Oligopilot is connected to a computer. So software is vital to using this type of equipment, and software is a whole other can of worms for both preservation, interpretation, and exhibition. How do we keep software available for scholars and do we share it with visitors?

If we were to build a museum to showcase this history what would we collect? What artefacts, what stories would we collect, who would we be telling them for?

Let's consider an alternative object, what about a Controlled Pore Glass Column? Benefits of this are it is very cheap, very small, easy to put on a shelf.

Marv. So if you look at that Oligopilot, that's a large column for making DNA. If you look at these little CPG columns where you have a few milligrams of Controlled Pore Glass, and in that previous column you've probably got 15-20 grams.

How do you get a lay person to a museum excited about CPG?

Anonymous 1. The problem there is, in chemistry, if you're a chemist, you go in in the morning, you put A together with B, and in 5 minutes you have something, and then you spend the rest of the day purifying. With this, the product, is attached on a bead, so you just filter out and save yourself a day of purification.

This seems like a very good example of how the day-to-day work of science has changed, and how something as small and seemingly mundane as CPG can have a huge impact.

Jeff Johnson

Factors shaping research in synthetic-chemical biology in the post-war West-German context (1945–1990): Report on a work in progress

I am primarily a historian of the social and institutional context of science. What I will try and explain is why the Germans were not more central to the history of DNA synthesis. We mostly hear about the UK and the US, but what's happening with the Germans? There are a number of factors that might help to explain what was going on, including the influence of industry, politics, history, and particularly National Socialism. They all created a culture that was in many ways intended to retard the development of this field.

I want to start with the academic-industrial connection in the postwar era. From the last third of the nineteenth century the Germans were famous for developing a remarkably successful academic-industrial symbiosis, in the dye industry and early pharmaceuticals in the form of organic compounds. So you had companies like Bayer, BASF, and Hoechst, that dominated the market for those simple organic compounds back in the early twentieth century. After the war, what was going on? I looked at a couple of the key German biochemists and their relationship to industry in the immediate postwar era. These are Richard Kuhn and Adolf Butenandt, both of them directors of highly prestigious

Fig. 9. Slide highlighting key developments in the organisation of biochemical research in Germany in the late twentieth century. Slide produced by Jeff Johnson, who also provides permission for its reproduction here.

Kaiser Wilhelm institutes, the predecessor of today's Max Planck Society, which sponsors a total of around 80 institutes in various fields. These are focussed on research with no obligations to teach. The myth goes that all of these people do just basic research without attention to applications. I have found that in both of these individual cases, right after the war it was feared that they would out-migrate, because the conditions in Germany after the war were so devastated, and finances so limited that they were both entertaining lucrative offers, particularly the United States was a possibility. Kuhn could have gone to the University of Pennsylvania with a lot of funding, and there were companies such as Wyeth laboratories, willing to support his work on areas of interest to him. For example, in regard to the immune factors that he was finding in breast milk, Kuhn was collaborating with one of the Penn professors (Paul György in the medical school) who had been an immigrant from Germany but had formerly collaborated with him in the 1930s before the Nazis took over. In conjunction with his work with György, Kuhn had a consulting contract with Wyeth (through its parent company, American Home Products) until 1955.

The Director of the Bayer pharmaceutical division, Heinrich Hörlein, after the war took it as his job to help restore German success in biochemistry. So he arranged industrial subsidies for both Adolf Butenandt for very large amounts at the time (approximately US $36,000 annually for several years from 1949), and also a smaller subsidy for Kuhn, to ensure that they would decline calls from abroad and remain in Germany. Both of them also had lucrative consulting contracts with industry which in my view may have helped keep their attention on the kinds of small molecules that could be manufactured in these companies, rather than looking at biologically active molecules which required production technologies that we think of today as genetic engineering, but which in the 50s few Germans were thinking about.

One question we can ask is 'to what extent were the Germans really responding to the new kinds of technologies that were emerging in the United States and elsewhere?' I am not sure that they were, even in 1973 when they brought together three Max Planck Institutes and made a massive complex for biochemistry in Martinsried, outside of Munich. They had 11 different departments, and that was soon expanded.

They were doing all sorts of things, but to what extent were they doing the kind of fundamental work in recombinant DNA and other things that led to Nobel prizes elsewhere? I have not been able to look at all the data yet, but they seem to be focussing on other questions, and this was in part because the German biochemists had not yet been able to make the transition into a closer relationship to molecular biology. Even the Institute that one would expect to be doing this, the Institute for Molecular Genetics, it had the problem that it was a descendent of the 1930s Institute for Anthropology, which had been associated with Nazi racism and experimentation. The claim I have been hearing is that association with chemistry helped these groups distance themselves from their status as the heirs of Nazi past. So it was in many ways a negative motivation to be doing molecular genetics, which had impact on their overall funding success and public relations. (Note from September 2018: my subsequent work has revealed that the leading scientists who were planning the Max Planck Institute for Biochemistry at Martinsried in the late 1960s discussed the possibility of locating the future European Molecular Biology Laboratory (EMBL) in their complex. The EMBL's planners chose instead to locate the EMBL in Heidelberg, but physically separate from the Max Planck Institute for Medical Research. The new Heidelberg EMBL was not completed until 1978, however, five years after the Martinsried MPI).

What about contrasting with the kinds of devices produced by ABI? If we look at a brochure from the MPI for Biochemistry in the late 1970s, we see instrumentation such as an automated protein sequencer from the Department of Protein Chemistry, which could sequence peptide chains with 50-60 amino acid components. Were any of the people there, people who could have potentially collaborated with business people to found something like ABI in Germany? Or were there cultural issues that kept them separate? As I said before, the industrial people were focussed on other kinds of products and were not so much interested in trying to develop automated processes for DNA sequencing and synthesis.

What about someone who seems to be talking about precisely that kind of biotechnology industry? Consider the example of Ernst-Ludwig Winnacker, who to my knowledge was the first person to introduce the term 'synthetic biology' into the German language, though if you go back to 1915 you had Emil Fischer, the Nobel prize winner, using the term 'synthetic chemical biology'. I asked Winnacker if he had read Fischer's papers, but he didn't think he had been influenced by that. In 1983 Winnacker did use the term 'synthetic biology' specifically to describe DNA synthesis. What's interesting is that he used this in the English form in quotation marks, as if he had got it from somebody else. We know he studied abroad and was actually in Berkley, so I'd be interested to know if people in Berkley maybe in the 70s were using language like synthetic biology at that early point.

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Winnacker was the man who as professor at Munich University founded the LMU Gene Centre in Martinsried in 1983-4, ten years after the founding of the Max Planck Institute there. The difference is that this was a university institute and for the first time offered a formal connection to allow the Max Planck people to have more access to students, which would then allow them to train the next generation. The MPI had groups, called *Nachwuchsgruppen* (next-generation groups), which were for developing young scientists, but I am still unclear about their formal connection with the university after 1973. Butenandt

and his MPI colleagues taught in the LMU medical faculty, because Butenandt was simultaneously professor and director of the university institute for physiology chemistry, as well as director of the MPI. After Butenandt resigned his professorship in the LMU to become president of the MPG in 1960, however, MPI-LMU relations were no longer as close. The subsequent move to the remote location in Martinsried would have further disrupted the MPI's ability to train doctoral students who could then reproduce and further develop new research techniques. Winnacker helped to restore the connection to the university.

I also wanted to look at the politics. So in the early 1980s, just as we have the take off of ABI and the biotech industry in the US, in Germany they were fighting over the dangers of genetic engineering. The Green party really took off in 1983, when they won their first Bundestag seats, by incorporating attacks on genetic engineering into their policy. And they got even more votes in 1987 following a few important publications. One was Benno Müller-Hill's book *Tödliche Wissenschaft* (Murderous Science), in 1984, in which a geneticist who had trained in the United States in DNA technology exposed the fact that a lot of his colleagues were essentially Nazis who had covered up their past. This was not good for public relations for bioscience in Germany. In addition you then had the Bundestag Commission, in which Winnacker played an active role, on 'Chances and Risks of Gene Technology'. Around the same time the Bhopal disaster had a very negative impact on the reputation of the chemical industry. Ultimately in 1990 came the first German law on genetic engineering which focussed on the use of a regulatory commission, similar to NIH, but much more elaborate. They had to approve every application, all done by the Central Commission on Biosafety, for experimentation on genetically altered organisms and the release of GMOs into production and the environment. I think this had a stifling effect in Germany.

Bayer, for instance, really moved all of their active research to the United States. They preferred to stay outside of their country when working on genetic engineering or genetic diagnoses, in part because of the PR problems involved.

> *Marv.* There is no question that this Green movement in Germany set back German science, no question about it. You couldn't go there and learn anything new in modern molecular biology, they couldn't do it, because it was against the law to do any recombinant research in Germany in the 70s, 80s, and 90s. In fact all the major pharma and chemical companies set up labs in the US to do their research components. They abandoned Germany.

I was in the Bayer archive, so was able to get their data on the research facility they opened in 1988 in West Haven, Connecticut (near Yale University), through their American subsidiary Miles Laboratories, but I would love to find out about the other companies.

Robert Smith

Visions of value and the making of mega-chunks

What kinds of social relations, patterns of work and technologies are being imagined and configured around DNA synthesis today? Are any of these distinct from the examples we have heard about so far? To begin to address these questions, I will focus on *Genome Project Write*, a proposal made by prominent scientists to synthesise the genome of organisms such as mammals, including humans.

Methodologically, I am building on information drawn from (very early) qualitative analysis of publicly available documents, technical articles, videos and recordings of events and workshops that have been run by the Engineering Life team, as well as my own notes from participation in the GP-write project, most recently as a member of the Ethical, Legal and Social Issues Advisory Group.

GP-write is a project 'in the making'. It is, arguably, more of a vision or phenom-

enon than a realised project. A quick look on the website and related reporting will draw your attention to questions about whether the object of synthesis is a human genome, whether or not that goal should be represented in the name (*H*GP-write or GP-write), about whether this is a single project or a consortium of different projects and partners, or even whether it is a 'Grand Challenge'. It is so early in the making that none of these things are stable and it is unclear what actors will coalesce or what project will emerge. I want to propose that there is utility in studying such emerging phenomena because it might allow us to ask what synthesis is for – what kinds of work is required, what kinds of social order are produced, what kinds of benefits might emerge and for whom, what kinds of culture might produce all of these things? And, importantly in the workshop context, what kinds of synthesis are being imagined and put to use?

At the outset it's important to acknowledge that there are substantial challenges with studying contemporary phenomena like this. One that is particularly relevant to this context is the notion of a 'politics of novelty' , which is a rhetorical switch that is often present when people talk about emerging science and technology. Synthetic biologists are particularly good at this. One example is Craig Venter's unveiling of the minimal genome in 2010. He goes to a lot of effort to emphasise that this feat was 'new': The team inscribed messages into the DNA to make it clear that what you see is *different*. But at other times people flip to talk about how what is being done is not really new, 'something we've been doing for centuries'. Acknowledging that there is a politics of novelty has several important consequences. One is that you can see immediately that language and the way that particular phenomena are framed is significant. Another is that this framing will vary in relation to different situations – the longer view is often adopted under situations of (perceived) controversy, for instance. A final important consequence is that historical scholarship will be vital to be able to tease apart contemporary phenomena.

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So, how do we 'know' GP-write? What kind of histories of GP-write are being told? I think two are visible.

↠ ***GP-write as Sc 2.0-2.0.*** One intuitive origin story builds on the lineage of genome-engineering projects that precede GP-write. These projects are generally told in terms of building capacity to synthesise larger and more genetically-complex organisms, as in the slide Jane presented. The most recent of these projects, Sc 2.0, is coming to an end and many of the most prominent people involved in Sc 2.0 are also involved in the proposed GP-write project. And much of the required technical infrastructure, namely the ability to synthesise and construct large chunks of DNA is imagined to be foundational for any GP-write project.

↠ ***GP-write as HGP-2.0.*** There are obviously many links to be drawn between the way people talk about GP-write and the way they talk about genomics projects more-widely. The synthesis and sequencing of increasingly complex organisms is one example. But the most striking parallel that was initially being drawn is in an origin story that connects GP-write to the Human Genome Project. Much has, obviously, been written about this project and there are many histories to be told of it. And it is therefore worth asking which history of the HGP is being told by

proponents of GP-write. Here, the dominant narrative is one coupled to so-called 'Carlson Curves'. These are images, first articulated by Rob Carlson which map the cost per base against time for sequencing and synthesis of DNA. While sequencing has fallen, synthesis remains high. It is argued – reasonably –that huge transformations and societal benefits flow from this reduction in cost of sequencing. It is claimed that this fall in price per base pair was a direct result of the funding of 'a' Human Genome Project; thus, funding a second Human Genome Project, one to 'write', will produce similar benefits.

I started by emphasising questions about the relationship between GP-write as proposed, the kinds of cultures that it emerges from and the kinds of social ordering those proposals might do. This line of work emphasises that to 'get synthesis done' will mean enrolling a wide range of people, resources and money. Narratives and visions are central to this process. What can be said about these narratives in this vein? What are they doing?

One of the first, tentative, things that can be said is that these stories is that they are doing different, but intertwined, things. One origin story blends epistemic, organisational and technical histories. It helps to make GP-write a credible proposal by making it feasible. The other acts as a way of conferring value: If the HGP produced widespread societal benefit by driving economic reductions in sequencing costs, another (H)GP will do the same. But this second narrative is arguably one that is more about creating a visionary 'big science' project. Indeed, Andrew Hessel, one of the core members of the consortium, has been explicit about this in public talks and interviews.

A second thing is that they might enrol different organisms and in different ways. In the first narrative, one that locates GP-write as part of a string of genome engineering projects, there are many organisms that would be credible, obvious and scientifically valuable to choose from.

In this reframing I think what we might be seeing is an uneasy blending of the two origin stories to produce a third narrative, one which is about the value of synthesis more broadly, and one which partially rolls back from the human

But in the second, one that confers social value and is arguably a much more explicit attempt to create a visionary project, the human is *the* necessary organism. Of course, societies value these organisms differently and the point at which most people will have heard about this project is in relation to a 2016 meeting, an intentional attempt to build momentum by coinciding the launch of a *Science* article with an international meeting. Instead, for various reasons, it was reported as a 'secret meeting to talk about creating a synthetic human genome'.

This reporting ricocheted around the world, was described as a plan to create designer babies, has been interpreted by some in the project as a 'firestorm' and has had tangible consequences for the proposal. For instance, in the 2017 meeting organisers were very careful to foreground discussion around social, legal, and ethical issues, with an aim to make sure these things were part of the project. More interesting though are the consequences for the scientific components and the vision. HGP-write has been re-framed as (the arguably broader) GP-write. In this reframing I think what we might be seeing is an uneasy blending of the two origin stories to produce a third narrative, one which is about the value of synthesis more broadly, and one which partially rolls back from the human. I think, potentially, in this broader project there might be space for more diverse forms of synthesis than the cloud-lab highly automated vision attached to the HGP-2.0, but I think this may come at the expense of a discussion of the value of more widely putting DNA synthesis to work.

Jane. Could you clarify your very final point about the kinds of synthesis?

Robert. The narratives that are being told are also attached to different visions of doing synthesis. For example, in publications of the early Sc 2.0 work, which was the creation of one artificial chromosome, talks about how the synthesis work was done by teams of undergraduates. The more recent processes are synthesis, using a combination of yeast and machines to synthesise very large chunks of DNA. The vision of the human synthesis is tied, for example by Hessel, to a cloud-based foundry model. The work that each of these different approaches takes will be different and will do different things. Most obviously, the UG synthesis approach has a pedagogical aspect. But additionally, what kinds of questions are answerable by building an organism as opposed to a genome? One of the things that I want to do is separate out the different forms of synthesis. What kinds of questions are solved by building an organism as opposed to a genome.

Anonymous 1. Today companies can synthesise the mini-chunks for synthetic genomes, that is the easy part. The hard part is putting them together into the big chromosomes. And then for humans and mammalian types the next hard part is to methylate all that DNA and then to package it on histones. So there is more than just the synthesis itself.

Anonymous 1. I understand there is a Chinese group that is also trying to get together, even with the same GP-write name, do you know if there is any coordination?

Robert. I don't know what coordination there is but I think that there is a parallel geopolitical aspect that is worth unpacking in the narratives around these proposals. This kind of thing can happen with big flagship projects. So, for instance in Europe there is the Human Brain Project. But since its launch there have been like 30 flagship large projects that are all doing similar things with very little coordination. And in America there was the launch of the BRAIN initiative, which was a direct response to the Human Brain Project.

Anonymous 2. A question for Jeff. I have been interested in the agro industry in Germany, and the sources I have been mostly looking at are Syngenta, the Swiss company. I was reading that they had a large advantage due to the way the Third Reich impacted industry and Syngenta were able to fill this gap. So were they perhaps able to take over the role that Germany had before in Europe?

Jeff. I can't say too much about what was going on in Switzerland. One company certainly, Hoffman–La Roche, was subsidising Adolf Butenandt, so there were some connections between German biochemists and the Swiss. I also know Richard Kuhn had good relations with Ciba. The Swiss were certainly very conscious of what was going on in Germany.

Many of the papers have suggested the synergies between technological and scientific innovation, and how these changes often make it possible to make brand new markets. To what extent can these things be seen as determined by technology? My sense is that for these markets to develop it requires things to come at the right time, creating tools for people who may not know the possibilities, but somehow when the tool is presented they are inspired to think more broadly.

Jody. Robert highlighted this bifurcation of when we say something is new, to make an economic market, and when we say 'this is nothing new we have been doing it for thousands of years'. We say those simultaneously to two different effects, while masking questions we should be asking. There might also be something deeper, regarding the ability to understand historical precedent, and does it hide the extent to which economics is really driving almost all of this. What is valuable is often what is valuable to the state. If we look at the history of Justus von Liebig, to take an example, there are some interesting historical precedents for how we have thought about analysis and synthesis, which might help us rethink what is going on here in biological chemistry. For we might interpret what he was doing as chemical, but it was also clearly biological. He was also mobilising

large numbers of students to get his chemistry done, in ways that seem to mirror these contemporary biology cases.

Marv. On the ethics of synthesising genomes. We can now synthesise the equivalent of a human genome every day. One of these days in some place in the world they are going to start synthesising a human genome, and it will be unlike in the early 80s when the Asilomar conference was organised. In those days you dealt with North America, Western Europe and Japan and that was it. So if you get those countries to agree on a set of guidelines, you pretty much get all of them. Now if you look at the people working on the yeast genome, it's all over the world. So even if one country, or one group of countries come up with ethical standards for synthesis of the human genome, how do you deal with that on a worldwide basis? It's an important question that I don't know how to answer. It's tough but we could literally the synthesise the DNA for the human genome in one day.

Jody. One of the questions I was thinking about was scale. Is the ethical question that you can synthesise so fast, or is it about who we think we need to talk to the ethics about?

Jane. There was an international summit on human genome editing a couple of years ago, in 2015, and one of the challenges there was how do we have an international regulatory system. This conversation is happening in those spaces which overlap with DNA synthesis.

Jeff. And that conference did produce guidelines.

Marv. But with the Asilomar conference almost every country that was capable of doing recombinant technologies in the early 1980s bought off on the guidelines. But just try and do that today. With the exception of North Korea you can synthesise a human genome in almost every country in the world.

Jeff. That does raise some interesting possibilities that someone is potentially going to exploit.

Jane. One of the points of the choice of yeast is that it is a very simple organism, especially in comparison to the human, they have only managed to get three synthetic chromosomes into the cell and the cell is quite sick. Anonymous 1 also talked about the problem of methylation and the chromatin, I don't think it's going to be so easy.

Marv. You're right, it's not just DNA, but still.

Anonymous 1. There is a biosecurity and biosafety angle. So people trying to synthesise Ebola for instance. So if it's to send to a P.O. Box in North Korea, we won't do it, but if it's to send to the CDC in Atlanta, well we do it all the time. You can screen and understand intent from looking at the sequence. 80% of the companies that make DNA from scratch have signed an agreement where they screen every sequence. On the question of creating life, people are currently struggling with 500 genes. It will be a long time before we make a human from scratch. What will happen sooner is editing of humans. So we need to think of somatic mutations as one thing, and be much more careful about germline mutation. The whole idea of genetics is that we are all different, and we can't lose that diversity.

Jeff. Is there a set of general principles for deciding who gets what and on what grounds? There must be a large grey area when you are not sure.

Anonymous 1. There is a government defined database of sequences that are defined as dangerous. If someone orders one of those sequences the synthesiser has to screen the user, and if they are authorised to use it it is fine. So if they had a Professor from Harvard ordering smallpox, and they call the Dean and ask what this Professor is doing. If they say the Professor is working on something completely different from smallpox, then they would have a question. Most of the time, when they get a flag, like a toxin, they call them up and talk, and explain it is because the thing they ordered was a toxin and they go 'ah, we had no idea, thank you I will do something else'. But it's the government database which most people agree is the right database.

Alok. If I could write a sequence for a toxin grafting onto a protein, and disguising the amino acid sequence so that I got

1/10th of the scaffold of a harmless protein, how would you know?

Anonymous 1. Mostly you are likely to lose the activity. So even if you got it, it is unlikely to be more dangerous. Companies also spend a lot of time talking to government agencies, such as the FBI, about the spread of biological weapons. What they are really worried about is not how someone gets the sequence, the hard part is making a large amount, and weaponising it without killing yourself. It is really only states that are large enough to weaponise these things.

Alok. This works for large companies like you. But isn't it the case that as the machines and chemistry gets cheaper, people are going to be able to make more and more themselves?

Anonymous 1. It looks to me that DNA synthesis is moving towards centralisation. Less and less people want to have to synthesise themselves, they want someone to make it all cheaper and faster for them. The next pandemic is more likely to come from nature.

Marv. I think when it comes to large genomes it will always be large companies. But when it comes to smallpox you could do it with an ABI synthesiser and take a month making DNA.

Anonymous 1. But the hard part is to weaponise it. How to make a lot of it and spray it over a large area.

Attendee biographies

Dominic J. Berry

Dominic is a historian and philosopher of science, integrating methods and ideas from science and technology studies. He is a member of Jane Calvert's 'Engineering Life' project, which investigates the ideas, practices, policies and promises of biological engineering, with a particular focus on synthetic biology http://www.stis.ed.ac.uk/engineeringlife/home.

Dominic is pursuing a history of DNA synthesis in order to broaden the current historiography of biotechnology, and also as a way to integrate historical research into the study of very contemporary sciences. This historical work requires collaboration with historians of chemistry, technology and the life sciences and so he is particularly pleased to have the CHF as a partner for this workshop. The overall approach requires collaboration with scientists, sociologists, industry, and philosophers, and so he is very grateful for your participation!

Jane Calvert

Jane is a social scientist based in the Department of Science, Technology and Innovation Studies at the University of Edinburgh. Her current research project 'Engineering Life', funded by a European Research Council Consolidator grant, focuses on the ideas, practices, policies and promises driving the field of synthetic biology. Her research focus is the synthetic yeast project (*Saccharomyces cerevisiae* 2.0). She is also interested in the governance of emerging technologies, intellectual property and open source, and in interdisciplinary collaborations of all sorts. She is a co-author of the book *Synthetic Aesthetics: Investigating Synthetic Biology's Designs on Nature*, published by MIT Press in 2014.

David J. Caruso

David is the Director of CHF's Center for Oral History. His current research explores the relationship between government, private funding, and the development of biomedical research in the United States from the end of the 20th century through today; the modern history of biotechnology; and science and disability. He received his doctoral degree in Science and Technology Studies from Cornell University, where he worked on the history of American military medicine before, during, and after World War I, as well as the creation, dissemination, and use of automated external defibrillators in the mid- to late 20th century. He received his undergraduate degree in the History of Science, Medicine, and Technology from Johns Hopkins University.

Marvin H. Caruthers

Marvin H. Caruthers is a Distinguished Professor of Biochemistry and Chemistry at the University of Colorado, Boulder. A Guggenheim Fellow, Dr. Caruthers received his B.S. in Chemistry from Iowa State University, his Ph.D. in Biochemistry from Northwestern University, and completed his post-doctoral studies with H.G. Khorana at The University of Wisconsin and MIT.

Professor Caruthers interests include nucleic acids chemistry and biochemistry. Approximately 30 years ago, the methodologies that are used today for chemically synthesizing DNA were developed in his laboratory and incorporated into so-called gene machines for the purpose of synthesizing DNA used by biochemists, biologists, and molecular biologists for many research applications. More recently his laboratory has developed methods for RNA chemical synthesis and for the synthesis of

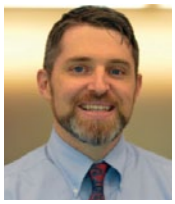
DNA/RNA on chips. His laboratory has also pioneered the synthesis of many new nucleic acid analogs that have found applications in the nucleic acid diagnostic and therapeutic areas.

He is the recipient of several academic and research awards including The Elliott Cresson Medal from the Franklin Institute, The National Academy of Sciences Award for Chemistry in Service to Society, The Prelog Medal in Recognition of Pioneering Work on the Chemical Synthesis of DNA, The Economists Award in Biotechnology for His Contributions in Automating the Synthesis of DNA, and The US National Medal of Science for 2006, the nation's highest distinction honoring scientific achievement. He is also the recipient of The National Academy of Science Award in the Chemical Sciences, The American Chemical Society Award for Creative Invention, and The Frantisek Sorm Medal, The Academy of Sciences of the Czech Republic.

Dr. Caruthers is an elected member of The US National Academy of Sciences, The American Academy of Arts & Sciences and a Corresponding Member of the German Academy of Science Gottingen. One of the co-founders of Amgen and Applied Biosystems, Dr. Caruthers remains active in the Biotechnology arena – most recently as a co-founder of Array BioPharma and miRagen Therapeutics.

L. Scott Cole

Scott is a 3rd year philosophy Ph. D student at the University of California, Davis. His areas of focus are philosophy of science, biology and technology. Prior to that, he worked in the corporate world, mainly for companies that developed and marketed technologies for life science research and medical diagnostics including Applied Biosystems, Agilent Technologies and Quest Diagnostics. He has a B.A. in Molecular Biology from UC Berkeley, an MS in Microbiology from Columbia University, and an MS in Management from MIT's Sloan School of Management.



Roger Eardley-Pryor

Roger is a historian of contemporary science, technology, and the environment. He earned his PhD in 2014 from the University of California Santa Barbara (UCSB) where he was a National Science Foundation graduate fellow at UCSB's Center for Nanotechnology in Society. Roger is currently a research fellow at the Center for Oral History in the Institute for Research at the Chemical Heritage Foundation. Roger's research explores ways that contemporary scientists, culture-makers, and political actors have imagined, confronted, or cohered with nature at various scales, from the atomic to the planetary. His newest project on "Ecotopian Visioneering" examines scientists who imagine a transformative and ecologically sustainable future; who then conduct scientific and technological research to enact and engineer that future; and who widely promote their visions and technologies to broader audiences—either to the public, to investors, or to policy-makers—all in effort to create a more ecotopian world.

Elihu Gerson

Elihu M. Gerson is a sociologist based in San Francisco. He has a BA from Queens College, CUNY, and an MA and PhD in sociology from the University of Chicago. His studies the organization of technical work, especially in the life sciences, where he focuses on patterns of alliance among specialties, including collaboration and intellectual integration. In recent years, his research projects have included a collaborative study of the Museum of Vertebrate Zoology at UC Berkeley; a study of an extended collaboration network centered on a unique colony of Spotted Hyenas at Berkeley; and observation of a biochemistry laboratory studying chromatin remodeling. He has also studied the organization of work in computing, and in hospital care of chronic illnesses. Analytically, he focuses on mechanisms of innovation in institutions and repertoires,

moving from uncertainty, variability and local specificity at daily work sites to reliable patterns of conduct at larger time and organizational scales.

Lijing Jiang

Lijing is a Haas Postdoctoral Fellow at the Chemical Heritage Foundation. Her scholarship focuses on how certain technological objects or materials for life sciences, such as the spawning goldfish, aging cells, or diagnostic balloons, shaped the scientific and social practice around them, mediating the interplays between biology and society. Her major project is a monograph on the history of making fish species, especially the goldfish, into experimental and model organisms in life science research institutions and aquaculture industry in twentieth-century China. She obtained her PhD in Biology and Society at the Center for Biology and Society, Arizona State University in 2013, and has held research positions at Princeton University, Nanyang Technological University, and Yale University.

Jeff Johnson

Jeffrey Allan Johnson is Professor of History emeritus at Villanova University. He received his PhD in modern European history and history of science from Princeton University and has also taught at SUNY-Binghamton University and as a guest instructor at the University of Bielefeld. Currently he is a guest scholar in the Research Group on the History of the Max Planck Society, Max Planck Institute for History of Science, working on the history of biochemistry after the Second World War. His publications in the social history of modern chemistry and the chemical industry include *The Kaiser's Chemists: Science and Modernization in Imperial Germany* (Univ. of North Carolina Press, 1990); *German Industry and Global Enterprise. BASF: The History of a Company*, co-authored with W. von Hippel, R. G. Stokes, and W. Abelshauser (Cambridge Univ. Press, 2004); *Frontline and Factory: Comparative Perspectives on the Chemical Industry at War, 1914–1924*, co-edited with R. M. MacLeod (Springer, 2006); and "The Case of the Missing German Quantum Chemists: On Molecular Models, Mobilization, and the Paradoxes of Modernizing Chemistry in Nazi Germany," *Historical Studies in the Natural Sciences*, 43/4 (Sept. 2013), 391–452. His contribution to the workshop is based on his current work on the role of chemists in the origins of modern synthetic biology and the technologies of artificial life.

Stephanie Lampkin

Stephanie Lampkin is the museum collections manager at the Chemical Heritage Foundation. Stephanie is responsible for the care, preservation, documentation, security, and storage of the museum's object and fine art collections. She also collaborates with other CHF staff members to digitize the museum's collections. She holds a PhD in history and a museum studies certificate from the University of Delaware.

Amanda Mahoney

Amanda L. Mahoney, R.N., Ph.D., is a Public History Fellow at the Chemical Heritage Foundation. A historian of nursing and clinical practice, her work at CHF focuses on the intersections of chemistry and the life sciences, the history of pharmaceuticals, and the construction of health data.

Erin McLeary

Erin is CHF's museum director. Prior to joining CHF, she served as an exhibit developer with the National Constitution Center and the Museum of the American Philosophical Society, and as a guest curator for the Mütter Museum of the College of Physicians of Philadelphia. She received her PhD in the history and sociology of science from the University of Pennsylvania and has published on the history of American medical museums, chemistry, and color theory.

Jody A. Roberts

Jody A. Roberts (PhD, Science and Technology Studies) is director of CHF's Institute for Research and managing director of CHF West. CHF's Institute for Research initiates, coordinates, and conducts research at the core of CHF's mission to foster dialogue on science and technology in society. In this capacity Roberts oversees CHF's Centers for Oral History and Applied History and ensures that research at CHF bridges the institution's unique ability to speak through museum exhibitions; live, print, and digital programming; and CHF's unparalleled collections in the history of science. The goals of our work are to develop the methods and tools that experiment with the unique capabilities of the science humanities to contribute to a more inclusive conversation about the place of science and technology in our lives; to share those tools with our peers; and to cultivate and mentor a new generation of science studies practitioner capable of taking these ideas out into the world.

Since joining CHF—first as a visiting fellow (2005–2007) and then as staff (2007–)—Roberts has experimented with ways in which we bring the intellectual core of science studies into the operations of a public-facing institution. Projects such as From Inception to Reform: An Oral History of the Toxic Substances Control Act and Sensing Change provided early templates for thinking about how we can open new conversations on topics that often seem impenetrable, hidden, or too politically charged. More recent and ongoing projects, such as REACH Ambler, have taken these lessons and continued to experiment with ways in which histories of the present provide platforms for speaking about possible futures.

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Robert Smith

Rob works in the field of science and technology studies. His work explores the social and ethical dimensions of the biosciences, primarily in relation to science policy, research funding and laboratory science. As part of the Flowers Consortium (at King's College London) and the Engineering Life project (at the University of Edinburgh) he is currently researching attempts to automate the practice of synthetic biology, the ways that interdisciplinarity and collaborations happen — especially between the social and natural sciences — and notions of value within research agenda setting, particularly in the context of 'grand societal challenges'.

Alok Srivastava

Alok is an independent scholar working in sociology, philosophy, and history of science in San Francisco. He obtained his Ph.D. in Biochemistry and Biophysics from MIT. His Ph.D. research focused on studying the structural aspects of protein folding as it pertains to engineering proteins for stability and function. He has been working in the biotechnology industry and was involved in projects developing an ultra-sensitive bioassay platform based on Bio-Micro-Electro-Mechanical Systems (Bio-MEMs) employing acoustic sensors, and a discovery platform for ultra-specific biomarkers for early detection of cancers based on aberrant Post-Translational Protein Modifications proteins in cancer cells. His current project in industry involves building an online platform for collaborative problem solving to support clinical treatment planning for uncommon cases in cancer.

Dr. Srivastava's research interests in sociology of science focuses on the processes of change in scientific capacities of laboratories and research communities engaged in multi-disciplinary and integrative projects. He is studying these problems through a series of historical case studies in chemistry, biochemistry, molecular biology, synthetic biology, integrative medicine and related areas.

Questions that inspired the workshop and which were circulated to participants

- How could biologists specify and create DNA sequences before the chemical approach was an option? What practices did this involve?
- How have biological, chemical, and engineering knowledge contributed to the development of DNA synthesis and its expansion into an industry? Not just their knowledge involved?
- Did the chemical synthesis of DNA teach biologists/biochemists anything about biological phenomena, for example, about synthesis processes within organisms?
- Who/what were the first companies or organisations to offer synthesis to order, or offer synthesis machines?
- When is DNA a tool? A product? A puzzle?
- How could a museum collect the history of DNA synthesis?
- What are the relations between organisms in receipt of synthesised DNA and those inheriting DNA through biological reproduction, or receiving it from another organism?
- How is synthesis influencing the biological sciences? Or the biological sciences influencing synthesis?
- What are the limitations for synthesis?
- What new social relations does the capacity for gene and genome synthesis produce?
- How are synthesised nucleotides used in research, be it for scientific or industrial purposes?

Programme

Tuesday, 28th November. Venue: CHF.

9:30–10:00	Coffee and registration
10:00–10:20	Dominic Berry: Welcome and introduction
	Session 1: Whole genomes/organisms
	(two 20 minute talks and 30 minute discussion)
10:20–10:40	*Alok Srivastava & Elihu M. Gerson*
	Synthesis of Viable Genomes and Organisms: Understanding Wholes
10:40–11:00	*Jane Calvert*
	Synthetic yeast: a tale of sixteen synthetic chromosomes
11:00–11:30	Questions and discussion
11:20–11:45	Coffee
	Session 2: Extending synthesis
	(two 20 minute talks and 50 minute discussion)
11:45–12:05	*L. Scott Cole*
	Selling DNA Synthesis: Applied Biosystems' DNA Synthesis Business from 1989–1992
12:05–12:25	*Marvin H. Carruthers*
	The Chemical Synthesis of DNA, RNA, and Certain Analogs
12:25–13:15	Questions and discussion

13:15–14:00 Lunch

14:00–14:20 *Erin McLeary, Stephanie Lampkin, Amanda Mahoney*
The material heritage of DNA synthesis?

Session 3: Epistemics of synthesis

14:20-14:40 *Jeff Johnson*
Factors shaping research in synthetic-chemical biology in the postwar West-German context (1945–1990): Report on a work in progress

14:40-15:00 *Robert Smith*
Visions of value and the making of mega-chunks

15:00-15:30 Questions and discussion

15:30–... Wrap up and final thoughts

Submitted abstracts

Jane Calvert

Synthetic yeast: a tale of sixteen synthetic chromosomes

The synthetic yeast project is an international effort to comprehensively re-design and construct the genome of the yeast species Saccharomyces cerevisiae wholly from laboratory-synthesised DNA. The dual aims of the project are to learn more about yeast biology and to develop improved yeast strains for industrial use. Many changes are being made to the genome to further these aims, including removing repetitive regions of DNA, constructing a 'neochromosome', and building in the ability to evolve the yeast on demand. Questions arise about whether the completed synthetic yeast—known as *Saccharomyces cerevisiae* 2.0—will be a different species from the wild-type.

Unlike other branches of synthetic biology, which focus on building discrete genes or genetic circuits, the synthetic yeast project is an example of construction at the whole genome scale. It follows in the steps of previous viral and bacterial whole genome synthesis projects, but is approximately an order of magnitude larger. The size of the project requires an internationally distributed effort, involving the coordinated activity of eleven labs across North America, Europe, China, Singapore, and Australia. The sixteen chromosomes are distributed around this international consortium.

This presentation draws on interviews with members of the project consortium, and visits to the different laboratories. Although all the synthetic chromosomes are designed at the PI's laboratory in NYU (with the exception of the neochromosome), the individual laboratories have pursed different synthesis and assembly strategies. For example, in Tianjin, China, one of the chromosomes was entirely synthesized by an undergraduate class as part of a 'build-a-genome' course. These different chromosomes also have different qualities and characteristics, and the scientists often refer to these to identify their 'favourite' chromosome. In addition, several of the laboratories are starting to design their own novel, bespoke chromosomes.

Some hope that the synthetic yeast project marks the start of a new era of whole genome 'writing' projects, which will involve the synthesis of the genomes of a range of species, including the human. Whether or not this initiative progresses as planned, I argue that whole genome synthesis projects would benefit from increased sociological, historical and philosophical attention.

Marvin H. Caruthers

The Chemical Synthesis of DNA, RNA, and Certain Analogs

The chemical synthesis of DNA/RNA dates from the mid 1950s in the laboratory of Sir Alexander Todd. Shortly thereafter Gobind Khorana pioneered the use of synthetic DNA/RNA for solving various biological problems such as the genetic code and the use of sequence defined oligonucleotides as templates for DNA/RNA polymerases and to solve biological problems including the synthesis of genes and studies on how proteins recognize DNA/RNA. Following this initial work, Bob Letsinger developed an entirely new synthesis methodology that was used in the initial DNA sequencing methods from Sanger's laboratory and

for synthesizing the human insulin and human growth hormone genes—developments that led directly to the establishment of the biotechnology industry. A brief review of these methodologies and some of the lessons learned about pioneering basic research will be discussed.

From 1977–1982 Professor Marvin Caruthers developed the use of nucleoside phosphoramidites as stable monomers for the solid phase synthesis of DNA and RNA. This ground-breaking chemistry was far superior to anything at that time and, even today some 35–40 years later, remains the methodology of choice for synthesizing DNA/RNA. Its chemical accuracy has enabled it to be deployed from the micromolar scale of DNA oligomer preparation for various clinical applications down to microdot, nano-scale chemistry that is used for numerous biological, biochemical, diagnostic, and chemical applications. Currently and in collaboration with Agilent, Prof. Caruthers has adapted this chemistry to the synthesis of DNA on glass chips (244,000 DNA segments per chip at 200-300 nucleotides in length/segment). For many different research applications, this on-chip process is performed at the level of 6 to 20 billion nucleotide condensations per day (the equivalent of several human genomes of 3 billion base pairs). Moreover, this work is now at the core of current DNA and RNA sequencing technologies. Modern biology could not have achieved its explosion of discovery over the last 40 years without the near-flawless phosphorus chemistry that the phosphoramidite methodologies have delivered to science and technology.

Notwithstanding the tremendous success of this basic phosphorus chemistry, Prof. Caruthers continues to develop the chemistry of key P(III) species for new purposes. If time permits, the synthesis of a new analog called thiomorpholino DNA will be discussed and certain initial biological results will be presented.

L. Scott Cole

Selling DNA Synthesis: Applied Biosystems' DNA Synthesis Business from 1989–1992

From its founding in 1981 until its acquisition in 2008, Applied Biosystems' Incorporated (ABI, Foster City, CA) was the leading supplier of instrument and reagent platforms for life science research. In 1985, the company introduced the Model 380A DNA Synthesizer, its first commercial platform for phosphoramidite-based DNA synthesis. Over the next several years, a combination of improvements in both DNA synthesis instrumentation and reagents enabled the company to achieve a dominant position in the DNA synthesis market worldwide. In this talk I will provide a commercial perspective on oligonucleotide synthesis based on my experience as Product Manager for DNA synthesis at ABI from 1989 through 1992. This was a time at which the need for synthetic oligonucleotides was growing rapidly, primarily based on rapid growth in the use of the Polymerase Chain Reaction (PCR). I will discuss ABI's entry into the DNA synthesis market, the competitive landscape at the time, how the company's DNA synthesis team was structured and how it operated, and I'll provide a sense of ABI's corporate culture at the time.

Jeff Johnson

Factors shaping research in synthetic-chemical biology in the postwar West-German context (1945–1990): Report on a work in progress

The purpose of the present paper is to examine some of the factors affecting the political, institutional, and scientific context of research in synthetic-chemical biology in postwar West Germany, 1945–1990. It is well-known that the West-Germans were considerably behind their colleagues in other western nations (particularly Britain, France, and the United States) in taking up the challenges and opportunities posed by the postwar development of molecular biology and the various technologies leading to genetic engineering. In some ways this is a surprising phenomenon, because at least until the 1930s the Germans had been among the world leaders in a field that I will designate as synthetic-chemical biology, using the terminology of Emil Fischer in 1915; unaware of Fischer's earlier terminology, Ernst-Ludwig Winnacker introduced the term "synthetic biology" into the German context in 1983, applying it specifically to the synthesis of genes.

Obviously one of the critical factors affecting the German situation was the impact of National Socialism, not only its purges of German scientific institutions but also the destruction brought about by its failed war of conquest. Beyond these factors were others inherent in the post-Nazi German context of the mid-20th century. In this paper, I would like to examine some of these factors by looking at specific examples of German organic chemists and biochemists in their institutional contexts, considering both the elite Max Planck Institutes (such as the MPI for Biochemistry in Munich and the MPI for Medical Research in Heidelberg) as well

as university institutes in related fields. I am also interested in considering the extent to which the German chemical and pharmaceutical industry in the postwar era continued its decades-old tradition of promoting close academic-industrial collaboration. Finally, I would like to examine the political context, including German debates over the ethics and risks of biotechnology and genetic engineering during the 1980s. When Winnacker introduced the term synthetic biology, the German debate was just beginning; it culminated in 1990 in the first German Genetic Engineering Law, whose origin should be seen in the light of the historical and cultural burden of Nazi atrocities.

SHI Curatorial team

The material heritage of DNA synthesis?

What is the material heritage of DNA synthesis? In this interactive session, workshop attendees and CHF museum staff will collectively imagine a museum of DNA synthesis. What artifacts would be displayed in this museum? What stories would those artifacts tell? For what audiences should those stories be told? And what would it take to move from an imagined museum to a collecting initiative that acquires and preserves the material heritage of DNA synthesis?

Robert Smith

Visions of value and the making of megachunks

This workshop addresses DNA synthesis as historiographically neglected. Today DNA synthesis seems to be going through somewhat of a resurgence. For instance, in Britain the UK taxpayer has indirectly contributed more than £150m to synthetic biology projects. Included in this figure is roughly £17,528,700.00 towards six so-called 'DNA foundries'. In the United States the Broad Institute has recently been awarded a five-year, US$32 million contract from the Defense Advanced Research Projects Agency (DARPA) to design, fabricate, and test large DNA sequences at scale. Similarly, and with much bombast, a team with George Church, Jef Boeke and Andrew Hessel have proposed a new grand challenge—the synthesis of large scale chunks of DNA—accessible for the modest price tag of £500m.

The rhetoric surrounding many of these investments is unsurprising to anyone following new and emerging forms of knowledge production and technology creation. And yet at the same time, past work has shown that such claims are not isolated or detached from reality. Perhaps the most blunt example one can give is to point to the fact that claims about future value are excellent ways to enrol people into a project. We should then pay analytic attention to claims about the purpose of doing DNA synthesis and the ways that they are built into websites of objects, people, places, and values.

In this talk I will take a first pass at doing just that. To do so I will draw on early reflections from on-going documentary work and observational material at synthetic biology conferences around the world. I will examine the cultures that such narratives claim to produce, the values that they embed and the significance of these things, both for life as we know it and for the social and human sciences as we relate to the natural and physical sciences.

Alok Srivastava & Elihu M. Gerson

Synthesis of Viable Genomes and Organisms: Understanding Wholes

This paper explores some issues raised by the synthesis of complete functional units – genes, pathways, biochemical complexes and the extension of this work to the making of autonomous wholes such as viable genomes and cells. Synthesis experiments generate a unique kind of understanding, achieved by de-composing and re-composing functional units. Such efforts directly address the descriptive and interactional complexities of biological systems and their constitutive mechanisms.

Synthesis experiments interpret mechanisms by demonstrating that articulated parts, refined and reassembled, behave as we expect them to. Synthesis experiments reveal and mark gaps between the explanations and manipulative results, and help specify the efforts to fill these gaps.

In synthesis experiments, scientists must learn to deal with incomplete systems that are not (yet) complete or viable. Laboratory procedures act as scaffolds that provide functional support for intermediate stages of construction. For example, a database containing the sequence of bases of a full bacterial genome keeps the order and content of the organism's genome while it is being chemically synthesized and biochemically assembled. This computer file thus functions simultaneously as a scaffold for the genome under construction, and as an important part of the laboratory's work organization.

The laboratory thus acts in place of the cell, supporting and enabling the assembly process by de-

veloping and deploying a set of protocols that specify needed resources and context to the incomplete system. These protocols also serve as bookkeeping devices that mark the parts of explanation(s) that are not yet realized as manipulation capacities.

Synthesis thus operates by mapping and tracking the relationships between de-composition procedures and corresponding re-composition procedures. Making and testing complete functional units enforces a reconciliation among the different groups of procedures. It is useful to understand synthesis experiments as explaining biological systems by carrying out re-composition experiments corresponding to de-composition experiments. A particular kind of understanding is achieved by these full cycles of de-composition and re-composition experiments of functional units and autonomous wholes that directly address the descriptive and interactional complexities of biological systems and their possible mechanisms.