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RESEARCH REPORT

The Structural Genomics Consortium

A knowledge platform for drug discovery

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Summary

This report presents the results of an independent evaluation of the Structural Genomics Consortium (SGC), conducted by RAND Europe with the Institute on Governance. The SGC is an open access public-private partnership (PPP) with a primary focus on pre-competitive structural biology research (namely determining the 3D protein structures) and an emerging secondary focus on chemical probes and antibodies, and epigenetics research. The SGC's current funding phase ends in June 2015 and this evaluation was commissioned to feed into discussions regarding the next stage of funding.

The evaluation had a number of objectives. Firstly, by drawing on a literature review, it aimed to establish the role of the SGC within the wider drug discovery and PPP landscape, assessing the merits of the SGC open access model relative to alternative models of funding R&D in this space, as well as the key trends and opportunities in the external environment that may impact on the future of the SGC. Secondly, the evaluation turned to key informant interviews with SGC researchers, past and present funders and external stakeholders, and a survey of SGC researchers. The objective was to establish – as the SGC nears the end of its current funding phase – the incentives and disincentives for investment, strengths and weaknesses of the SGC's model, and the opportunities and threats the SGC will face in the future. This process enabled us to assess the most convincing arguments for funding the SGC at present; important trade-offs or limitations that should be addressed in moving towards the next funding phase; and whether funders are anticipating changes either to the SGC or the wider PPP landscape. Finally, we undertook a quantitative analysis to ascertain what judgements can be made about the SGC's past and current performance track record, before unpacking the role of the external environment

and particular actors within the SGC in developing scenarios for the future.

Literature review

The literature review covers the conceptual background to open innovation, intellectual property and PPPs. In reviewing academic and grey literature a number of key findings can be identified. Firstly, the review found a vibrant critique of the status quo from a number of angles on the possible dangers of the 'anti-commons' and the potential benefits of a more collaborative approach to research and innovation. With regards to the question of whether there are initiatives that are comparable to the SGC, it is clear that the SGC is unique although it shares characteristics with a wide range of other 'open innovation' partnerships and collaborations; meaning that whilst it has unique characteristics, it is a part of a trend. Much of the grey and peer-reviewed literature suggests that this trend exists because there is a widely acknowledged crisis in pharmaceutical R&D. There seem to be two distinct trends emerging in pharmaceutical R&D. One is based on biotechnology, venture capital and intellectual property rights, and the other is based on more openness and collaboration at pre-competitive stage. There are grey areas where these two trends converge but the logic behind each of them is distinct. Finally, there are broad system level issues to do with the nature of the way science is funded and incentives in public and private sectors and different perspectives on what works.

To contextualise the conceptual arguments, the literature review included analysis of PPPs in the health sector and in other sectors. There are some initiatives which have similarities to the SGC both in terms of overall aims associated with contributing to drug development and in trying to foster more openness and collaboration in pre-

competitive research. There is also a set of initiatives that have a focus on structural genomics such as Japan's RIKEN research institution, the USA's Protein Structures Initiative (PSI), and Europe's Structural Proteomics in Europe (SPINE) initiative. Each of these groups is organised to deliver structural genomics information in different ways. We reviewed aspects of both with a particular aim of identifying any evaluations of these organisations that might help to inform both the evaluation and the nature of our findings and insights.

In considering comparators from other sectors we found a variety of PPPs including formal organisational models, informal networking mechanisms and different platforms geared towards facilitating innovation and knowledge production to the benefit of different sectors. A large number of initiatives are reviewed and summarised before a more detailed analysis of three selected 'case studies' are given for the Linux, Sematech and EU Technology Platforms initiatives. Our review found that PPPs from other sectors are mobilised in multiple ways and that their characteristics differ according to their geographical coverage, funding, sector, position in the value chain, innovation model and organisational focus. Most PPPs are evolving and transform over time; their characteristics depend on the maturity of the sector, the characteristics of industry and firms therein and wider political, economic, technological and scientific factors influencing innovation.

The SGC as a platform for knowledge

We drew on survey and key informant interview data as well as quantitative analysis to focus on three, interrelated yet conceptually distinct spheres of knowledge which emerge from the SGC's efforts:

- *The SGC as a model for investing in knowledge:* this sphere relates to what the motivations and rationale for investing in the SGC are from the perspective of those who are engaged in it, including funders, SGC researchers and external collaborators/stakeholders.
- *The SGC as a model for generating knowledge:* this domain relates to perceived strengths and weaknesses of the SGC model as it operates in practice.
- *The SGC as a model for extracting value from knowledge:* this domain relates to the value that

comes from both the investment and generation of knowledge.

We present our findings in relation to these spheres of knowledge in order to draw out a more nuanced discussion about the role of the SGC as a unique model for the production of scientific knowledge. We hope this framing moves the discussion away from the question of how the SGC might be funded in future, to that of how best to maximise the different ways stakeholders find the SGC model to be of value for them.

First, viewing the SGC as a model for investing in knowledge resulted in identifying incentives and disincentives for investing in the SGC model from the point of view of SGC researchers, past and present funders and external stakeholders in the wider chemical and biological science landscape. Incentives which were discussed across the groups covered a range of topics, including: open access, collaborative research and networks, 'de-risking' of new areas of science, the 'industrial' focus of the SGC and rapid and efficient research.

Open access makes the SGC unique as a PPP in this field and creates a number of desirable knock-on effects, including wider societal benefits, maximising the opportunities and efficiencies of further research, improving the competitiveness of the field, proving the feasibility of open access, enabling funding to be secured and enabling the efficient establishment of diverse collaborations. This latter point is particularly aided by the SGC's ability to overcome institutional regulations and restrictions about intellectual property due to its open access nature. Several examples of efficiency in the research process, improved research outputs, and new areas for drug discovery, were highlighted across the collaborators, funders and researchers we spoke with and all attributed this in part to the open access philosophy of the SGC.

The collaborative research opportunities and access to a global network in core areas of structural biology expertise were cited as key reasons for investment in the SGC by most researchers, the majority of the funders and some external stakeholders. One reason that the SGC's collaborative network is particularly appealing and, therefore, is an incentive for investment, is that one can easily make the most of the SGC's collaborative network because of the open access format. Several interviewees commented that this format means that it

is very easy to set up collaborations without worrying about contracts and legal issues. In particular, the majority of private sector funders stated that links to a global network of expertise in the area of epigenetics was especially important.

Many private sector funders highlighted the importance of the SGC model in helping to 'de-risk' new areas of science as a reason for investment. In particular, the majority of pharmaceutical funders used the epigenetics programme as an example of this 'de-risking' effort, and it was clear that the SGC's decision to conduct epigenetics research was a significant factor in their decision to invest in the SGC. Epigenetics is a new and developing area of biology and joining a consortium offered gains in this area at relatively little cost. Closely linked to the incentive of de-risking new areas of science is an incentive around the alignment with ongoing strategic initiatives within a company, public funder or collaborating organisation.

Many stakeholders cited as an incentive the fact that *the SGC enabled rapid and efficient research processes*. There are two elements to this incentive. The first is that the majority of interviewees felt that research happened more quickly in the SGC than in either academia or industry, and this was a significant strength of the SGC. The speed and volume of SGC research is enabled at least in part through open access, the collaborative nature of the model and the ability to collectively de-risk new areas. The second, related, element, was expressed by several funders, who reported the SGC's approach to using an *'industrial model'* for research was an important factor in their decision to invest in the SGC. The SGC possesses several characteristics of an industrial model, with milestones and targets determining the scientific outputs and a commitment to ensuring that findings can be reproduced by others. Not only this, but it operates on a large scale, accessing a wide range of expertise and resources which would not be available to a small laboratory. This is perceived to have a considerable impact on the efficiency and volume of SGC research.

Disincentives for investment as identified by SGC researchers, funders and external stakeholders included *unprotected intellectual property* of work conducted by the SGC and a *perception of limited spillover effects for the wider community*. Such regional and national spillover effects of the SGC are important to public sector funders in

particular who see these as linked to the SGC's physical location. However, it is important to note that a lack of economic and societal spillover effects was not cited as a weakness or a disincentive by all public sector funders and this difference in views demonstrates the difficulty the SGC has in meeting the needs of each individual funder.

The second reason for our approach is that viewing the SGC as a model for generating knowledge allows us to set out the strengths, opportunities, weaknesses and challenges of the SGC. These areas are interwoven with incentives and disincentives for investment to a certain extent; however in deliberately separating the two we hope to understand how far perceptions of the model prior to investment align with how the SGC operates in practice. Across the different perspectives in the evaluation a number of interrelated strengths and opportunities for the SGC were highlighted, including the role it plays in enabling collaboration and maintaining strong research networks; providing rapid and efficient research outputs and processes for the field; having an industrially oriented, flexible research model with strong leadership; and being able to produce strong, world-class science.

Along with world-class scientific expertise, the *extensive collaborations between academia and industry* were the most frequently mentioned strength of the SGC, across the three stakeholder groups. Indeed, it was a specific aim of the founders of the SGC to ensure that the benefits of public and private sector research were brought together in the most productive ways. In this, the SGC considered how the private sector could benefit from the consortium without involving intellectual property, as well as where the private sector could add value to the consortium aside from the provision of funding. This included their expertise in designing molecules or assays for target validation, their commercial focus which would help to drive drug discovery, and their need for reproducible science. Moreover, close collaboration and networks help to prevent the duplication of effort among pharmaceutical companies. If the SGC did not exist, these organisations might be more likely to pursue the same lines of discovery independently, underscoring the efficiency afforded by the SGC. Though we were not able to quantify this in this evaluation due to resource constraints, one can likely conclude that at least in some instances,

overall costs to both public and private innovation efforts would be higher in the absence of the SGC and thus there would be a negative impact on drug discovery.

Providing rapid and efficient research outputs was cited as a strength of the SGC across all stakeholder groups. Eighty-two per cent of surveyed researchers (N=17) believed their research had come to fruition more quickly through the SGC than it would have done if it had been supported by traditional academic approaches. The most frequently cited reasons for accelerated research translation were high quality collaborations and an integrated approach, the lack of a need to spend time writing grant proposals, and the efficiency of SGC processes. Other reasons which emerged from the interviews as to why people thought the SGC may be faster and more efficient at research were related to the lack of intellectual property, the importance of a highly interactive research process which is accelerated through open access, and the fact that the SGC is streamlined and narrowly focused, with a strong ‘company ethos’ and industrialised research processes.

One of the reasons that many stakeholders felt the SGC was able to operate more efficiently than other research models was its *industrially oriented, flexible model of research which is well managed with a clear focus* (unlike some academic research which may be more curiosity driven). The SGC’s flexible approach to collaborators enables a large range of diverse networks and collaborations, which in turn affords the SGC the chance to be flexible in approaching new scientific areas. The flexibility coupled with the focused nature of the science allows the SGC to exploit economies of scale and networks in exploring new scientific areas. Moreover, the leadership of the SGC was thought to be essential to making the SGC a success in practice. Related to this, is the fact that the SGC is able to conduct ‘reproducible science’ – that is, the SGC can be relied upon to produce results which can be reproduced by others. Although this may not be highly valued by academia (given that experiments in academia are rarely replicated), it is of particular importance to industry given that they cannot build technologies that work properly without it.

With these strengths come many opportunities. *The SGC is part of a wider trend which seems to be forging the way in pre-competitive research in the drug discovery landscape.* There is a real oppor-

tunity to expand the pre-competitive boundaries of drug discovery in the future. Not only are there broader changes in the field which mean that pre-competitive research is seen as more likely in future by stakeholders, but there is also a view that the SGC’s open innovation model is particularly appropriate given the structural biology focus of the SGC. In addition, several interviewees were explicit in their view that it was the role of the public sector to help ensure the future of open innovation and drive pre-competitive research boundaries as the private sector itself was not likely to provide a catalyst in and of itself. This is clearly a complex issue which will be shaped by a series of external factors, including price pressures, trends towards outsourcing innovation, openness to flexible approaches, the intellectual property regime and future downsizing in the economic climate.

These features of the SGC mean that it has a wide range of opportunities in terms of scientific areas of focus and *there was a degree of divergence among interviewees regarding how the SGC should exploit these opportunities in the future.* Some wanted the SGC to narrow their focus back onto structural biology, while others were of the view the SGC should continue to push into areas such as epigenetics. Ultimately the scientific direction of the SGC will be determined to a certain extent by available funding. However one of the most frequently cited weaknesses of the SGC was the fact that its mission had become much more diffuse in recent years.

Alongside the strengths and opportunities for the SGC, a number of weaknesses and challenges for the future were identified. These included: a view that there were too many collaborators, which inhibited the ability to do the science; a perceived lack of professional development opportunities for SGC researchers; too much movement away from the SGC ‘core’; and a lack of resources to support future growth. As above, we first present weaknesses in the model before discussing the challenges for the future.

The single most significant challenge mentioned across interviewees was *the need to maintain a substantial level of funding for the future.* Public sector funding has diminished significantly since the SGC’s inception and has been replaced with private sector funding, leaving a one to five ratio of public to private funding. However, there was considerable divergence among interviewees

regarding the importance of the source of funding. There was a shared view among all funders that the public sector/private sector mix was important. However, a public sector or 'non-industrial' presence was considered to be important by private sector funders for two main reasons. First, the presence of non-private funds would keep the SGC research open and in the public domain. Second, it would keep SGC research innovative and safeguard against SGC becoming too closely aligned solely with the needs and interests of the private sector. Non-private funds are seen as protecting the SGC from becoming more like a contract research organisation, which would result in its losing its competitive and innovative edge. Although the role of the public and private sectors were generally considered to be important, the role the two different funding types might play was debated. The role of each sector within the SGC is particularly important in understanding the consequences of public sector withdrawal, and this is built upon in more detail through scenarios in Chapter six and the overall conclusion.

Finally, viewing the SGC as a model for extracting value from knowledge, we provide a more quantitative analysis to ascertain what judgements can be made about the SGC's past and current performance track record. The quantitative outputs of the SGC range from the main outputs of SGC work (such as publications, structures and sequences), through to broader economic outcomes (including monetised outcomes) that are the result of SGC involvement in research. We identify a number of SGC's scientific knowledge outputs. Firstly, since 2004, the SGC has developed and deposited the structures of 1195 proteins in the Protein Data Bank (PDB). Secondly, from 2004 to 2011, this has led to 83 new sequences deposited in Uniprot – the protein sequence database. Thirdly, the SGC has produced 452 peer-reviewed journal publications (and eight books) up to August 2013. Finally, in terms of dissemination SGC scientists attended and presented at over 250 conferences from 2007 to 2011, including 38 poster presentations and 87 invited talks as a direct result of scientist involvement in the SGC.

In terms of economic outcomes our quantitative analysis shows that the average cost per structure identified for the SGC over the 2004/5–2012 period was \$289,000 CAD which suggests, compared to other structural genomics organisations,

the SGC is able to provide competitive cost per structure for the protein structures it does develop (especially bearing in mind the other outputs that the SGC produces in terms of clones, probes and vectors). When we compare this to other structural genomics organisations in the same time period, we can see that the SGC is considerably more efficient than RIKEN (\$712,000 CAD per structure – based on 2006–2011 funding for RIKEN as a whole), while the cost per structure for PSI (in its first two phases, 2000–2005 and 2005–2010) was \$104,000 CAD. The quantitative outputs do not account for other economic benefits arising from SGC activities (such as the patents and sales of products developed by industry partners downstream from their involvement in SGC research), which would provide an even higher likely monetary return on investment.

In undertaking an analysis of the quantitative outputs of SGC work it is important to recognise the context in which SGC operates the value of impacts arising from the SGC's work. Specifically, the SGC have set a specific task to deliver protein structures that go beyond those already developed in the scientific literature. This means that the SGC specifically targets proteins that are considered more difficult to work with, and therefore any consideration of the outcomes of SGC research should take into account the relative difficulty of the task the consortium has set itself.

The possible futures for the SGC

To inform how the SGC might look in the future we developed a set of the scenarios for the SGC to consider, which form the basis of Chapter six. For our scenarios analysis exercise we used a simple scenario development process rather than a more formal approach. This meant that we thought about the SGC in light of future decisions it may need to take about its funding strategy, scientific direction and the external context in which these decisions would need to be made. In order to do this, we first identified contextual certainties and uncertainties which would play a role in the future which included the nature of R&D in the pharmaceutical sector, the direction of drug discovery science, and wider political economic conditions. Allied to these contextual conditions we then identified a list of critical success factors for the SGC, permutations of which are likely to be particularly important to the SGC's future. These

factors included the SGC's scientific vision, business model, funders, role of open access, role of networks, spillover effects, location and consideration of wider scientific and political-economic developments.

When it came to developing the scenarios, we considered both the contextual elements and the implications of them for the success factors. We developed narratives around four scenarios, each of which was underpinned by the assumption that the SGC continues to function as a knowledge platform in the future with different drivers for generating knowledge, investing in knowledge and extracting value from knowledge. In the first scenario of *'Maximising the science'*, the main driver is about generating new scientific knowledge. Extracting value from that knowledge is of least importance, and the investment incentives derive from the open generation of publicly accessible scientific data. In the second scenario *'Maximising returns for industry'*, the main driver in the future concerns extracting value from knowledge, with the generation of knowledge playing the lesser role. Funders support the SGC to facilitate industrial development and competitiveness so that the value of SGC science can be maximised. In the third scenario, *'Maximising the good news story'* the main driver for the SGC is to lead to greater patient benefit and improving health outcomes. The main incentive in this scenario is not so much about value, but about generating knowledge that can catalyse direct returns for patients. The value of the SGC in scenario three is in the targeted nature of knowledge outputs in different disease areas. Finally, in the fourth scenario *'Maximising the benefits to nations'* we see the main driver being extracting value from knowledge as countries seek to invest in the SGC so that they can see a return on investment for industry through the creation of knowledge spillovers and economic growth. In this scenario SGC is supported by the public sector as a platform to create knowledge that will lead to economic benefits in terms of jobs and gross value added.

Each of these scenarios has its own merits, challenges and opportunities. They are presented as distinct, but in reality there are many overlaps between them to be further explored and examined. What will be crucial for the SGC going forward is the balance between the different elements in each model, and the extent to which different drivers serve as the motivating element. It

is important to note that in developing scenarios we sought to create a narrative and in many cases often exaggerated what the future might look like for the purposes of illustration. We fully recognise, and in fact would likely argue, that SGC's future strategy is going to encompass a mix of these scenarios, but it is the process of determining that mix which is important. In order to do this, we must understand what each scenario looks like independently.

In conclusion, our evaluation suggests that in order to understand the added value of the SGC, it is important not only to appreciate what the role of open access is, but also how both public sector and private sector actors within the SGC benefit and help to maintain it. Therefore, we argue that there is a finely nuanced role of the public and private sector presence in the SGC in relation to the added value it brings. The public sector plays a fundamental role in relation to maintaining open access, while the private sector helps to maintain the SGC's industrial quality and reproducible science. Both contribute to a form of innovation and related benefits that come out of the SGC and spill over to the wider field. Therefore, without each element, the SGC ceases to exist in its current form, and its added value to the field is reduced. We believe this goes to the core of some of the current tensions in the SGC model and its future. Therefore, by working through the role each plays, the benefits which accrue, and the broader questions and insights this leads us to, we hope to shed light on a possible way forward.

All of this serves to demonstrate that each set of funders, and the public sector in particular in relation to open innovation, needs to be fully aware of the role it is currently fulfilling and the losses that would be incurred if each were to withdraw from the SGC. These losses should be considered against the backdrop of the changing nature of drug development and innovation which poses wider challenges to the field.

The report ends with a list of recommendations for the SGC to consider in moving forwards. These are to:

- *Maintain the SGC in something akin to its current form*
- *Develop a high level strategy that provides a broad plan for operations over the next five to ten years*
- *Incentivise the public sector to (re)invest*

- *Develop a strategic approach for identifying potential philanthropic and charitable funders who may be interested in investing in the SGC as a platform for knowledge*
- *Consider ways to enhance the sustainability of the SGC's leadership, potentially through recruiting deputy leaders*
- *Provide more support for scientists to aid career progression and develop transferable research skills*
- *Improve monitoring and evaluation processes to more effectively capture knowledge and disseminate positive impacts where they arise*
- *Build on the successful examples of the few small biotechnology firms which have arisen out of partnering with the SGC to focus more on possibilities for engaging small firms in its generating knowledge and extracting value models*
- *Undertake a more comprehensive assessment of the comparative costs and merits of the different trajectories to drug development.*

We are conscious that some of the recommendations presented may not be in line with the SGC vision, but they arise from our understanding of the evidence gathered in this report, the different challenges and opportunities facing the SGC and how it may need to respond. These are important considerations for the question of how the SGC can attract more funding, generate knowledge more efficiently, and extract more value from the knowledge it creates in both the scientific and wider socio-economic sense and address the pressing issue of how the consortium can be sustainable in the future.