

THE DISCOVEROME

creative destruction of barriers for faster to patient medicines R&D

Future medicines discovery begins and ends with patients. Its scope will no longer be limited by the walls of the lab and the moats of major pharma. It will be disease-led, highly collaborative and fast. What is needed is not just new assays, technology and ideas. It is new organisations, influencers and shared working. A generation Y approach for generation Y times.

The shape of medicines R&D has transformed. Much like the story of Hollywood studios but at an alarming rate, the industry has shifted from an in-house institution to a highly-distributed, multi-party collaboration. This brings logistical benefits as well as challenges that are discussed elsewhere. The larger question for today, however is, does the work we do in discovery and early development adequately reflect patient's priorities?

This article lays out the model for a disruptive approach to medicines R&D, the discovery syndicate, or Discoverome. This is a consortium model built on valuable work from Faster Cures and significant input from research charities, translational academics, finance professionals and seasoned industrialists. It lays out some of the benefits and challenges of the model and its origin in a 300-year-old UK institution with global recognition. It also outlines the pivotal role that the new medicines discovery catapult plays in enabling this innovation.

Putting the patients first

The voice of the patient is rising in volume and vehemence. We will all be patients one day and shall be both the consumers of medicines and the experts in living with our particular disease. However, unlike almost any other modern industry, patient influence on products developed for their need is painfully small. Eric Topol's excellent *The Patient will see you Now* is a clear statement of how the power of the patient is growing at the delivery end of healthcare, but their impact on the R&D pipelines of major pharma and mainstream biotech remains lower than any other tech industry. In the UK alone, medical research charities spend more than \$1.5 billion per year on basic research. If this level of investment were funding b2c product development the impact would be immense, but in pharmaceutical R&D it remains a poor second to the voice of industry and academia. Both of these groups are – and must be – involved but, like the pig in the egg and bacon story, the patient is committed.

By Chris Molloy



The members of a drug discovery syndicate

Patient advocacy is now part of the mainstream but advocates often wonder aloud as to whether they are being presented or heard. Too often a patient advocate's place in the running order is at the end of the day, and their stories are accompanied by the muffled sound of roll-along bags as busy industry people leave to get their planes home. If the bravest advocates feel this from the podium then we are failing as an industry. Whether one looks at the world from an experience of disease or takes a biomolecular view, one thing is true: the answer is in the patient.

The work carried out by groups such as Faster Cures in the USA and the Association of Medical Research Charities (AMRC) in the UK are part of a movement to put the patient first. Both organisations know that patient-centricity will deliver a range of treatments, not all of them perhaps the ones that industry wants to make. They may be neither sexy science nor breakthrough biomarkers, but they are meaningful, impactful and, yes, valuable. The days when eminent science defined unmet need are gone. It is past time for change and the pressure is building.

Sometimes the patients let this frustration show, and when it happens it brings the audience back into line. The bags stop rolling, the iPhones (other devices are available) return to sleep and the patient is heard. At a recent meeting of the

Association of British Pharmaceutical Industry and AMRC a long-term arthritic asked the audience why the "...clever people in the room insist on calling my pain a co-morbidity. It's not. It bloody hurts". This type honesty and reality, heard more and more in rooms used to PowerPoint and pleasantries, is something that counts and must influence us as an industry to involve and then take meaningful action.

Medical research charities know that the time is right to become more translational on behalf of their beneficiaries. In the past many saw the funding of basic research as a low risk benefit to their patients. Increasingly this is now viewed as insufficient. The \$1 billion licence seen by the Cystic Fibrosis Foundation to Vertex also showed that consistent investment in translation, coupled with industry rigour, delivered patient benefit and financial value. Not all charities can and will do this, but the bow-wave is there. More charities are bringing in industry leaders to help them fund pipelines as well as professors.

However, there remain critical gaps and market failures standing between this will and broad success. These include industry-academic barriers, access to core skills, access to focused, long-term finance and the creative destruction of the barriers that keep patient need, biotech innovation and pharma delivery power apart. Overcoming these barriers requires stimulus, vision, energy and willingness to build a new set of patient-centred, commercial consortia. Enter the Discoverome.

The syndicate

Medicines R&D is a multidisciplinary, collaborative process, but to date the folks inside the tent have been industry and biotech. This has extended over recent years into academia – initially to outsource the risk of target validation and more recently for access to clinical samples and cohorts – and now extends further to a reliance on CROs as independent intellectual provider.

The therapeutics R&D industry of course contains a broad church of mega, multi-disease platform players through to highly-focused ultra-orphan companies. The analysis of Deloitte in recent years has indicated the focused, smaller companies gain more return from their R&D pipelines. Indeed, the top 12 mega-pharma with broad therapeutic coverage now returns less than 3.7% pa on its investment – an unsustainable crash from 10% in just six years. If (according to Deloitte) 'neither size nor M&A is a viable strategy' you do not need an MBA to work out that it is time for focus, longer-term thinking and getting engaged with the customer.

1. Stratification of disease is both biologically and commercially valid so we should develop our thinking around disease.

2. We should also consider that medicines discovery is about finding and proving a medicine. This is an activity that starts at the idea of a medicine and completes when you prove you have one: at a successful Phase II. This is what is relevant to patients and we need to develop a focused way to make sure we are thinking 'Fast to Patient' at every step, and in step with patients.

3. Medicines R&D is a long-term activity. Currently it takes an average of 6.5 years to translate a valid target to a Phase II proof of concept. To support and sustain the flow of medicines to patients a long-term structure is needed.

To achieve this, we suggest herein the creation of disease-specific syndicates. These syndicates are a disruptive combination of biotech, translational researchers, focused pharma and focused funders.

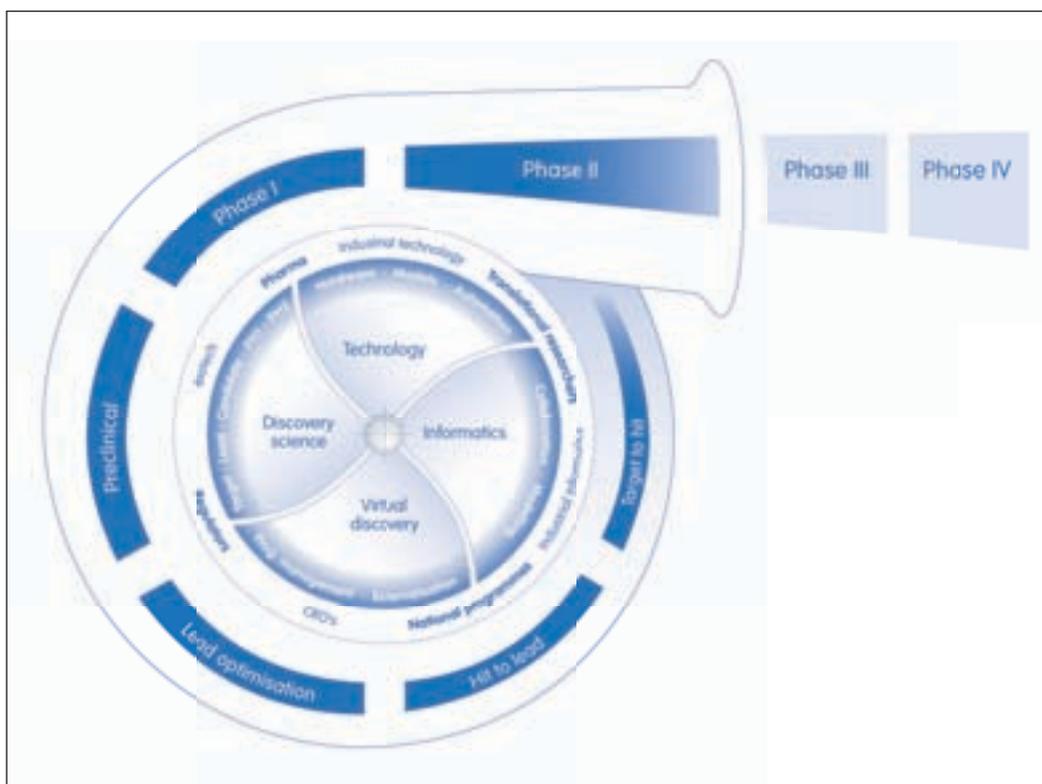
They are cornerstoned by a medical research charity on behalf of the patient and are managed by industry professionals, acting as agents and enablers. Working from target validation to phase

II, they will act to define the needs of patients with a commercial relevance; to translate the work many of the charities have instigated; to foster a portfolio of assets through joint, and independent, concept proof and into financeable form and; to drive collaborations where none exist today. These new consortia will play to the strengths of all without compromising their strengths.

Syndicate graphic?

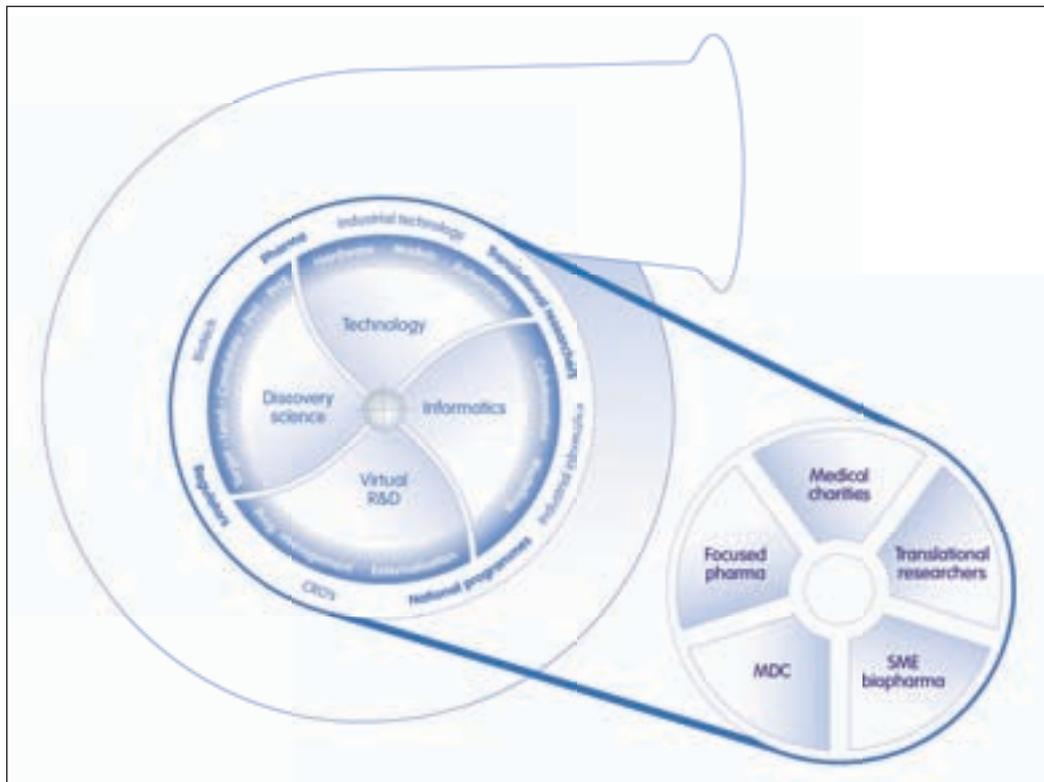
Built upon a corollary with the finance markets, multiple syndicates may exist reflecting the segmentation of disease and the ability of 'asset owners' to contribute to multiple groups. However, the focus of each syndicate will be clear. Anchored to the ground by, and for, the patient, and intent on translating every cent into long term value for them and the members of the syndicate.

The model is scalable, flexible and built upon principals long-proven in other syndicated markets such as Lloyds of London, the world's most famous insurance market. Lloyds is based upon the notion that financial investors with a long-term common interest in certain risk classes (oil rigs, ships, buildings etc) gather together, and through agents are able to manage their investments together, sharing upside and balancing risk. This pool of



The technology and externalisation engine of the catapult

The turbo that powers the syndicate



focused money is then brokered out to the world's risk in their areas of interest.

We suggest turning this on its head. Think about it for a minute. Imagine a group who have risk assets all focused in one disease, managed by industrially experienced agents able to help the group derisk and progress those assets smartly and efficiently. Imagine this syndicate of assets then brokered out to long-term money. Imagine then the sharing of upside across the syndicate, including the charity that cornerstones the syndicate. Truly commercial, assets-focused, patient-centred and sustainable.

The syndicates should exist in a safe harbour environment with access to an experienced governance and where the network is able to provide 'pop-up' expertise and independent managed services. The membership will be able to help each other and share in each other's commercial success.

Where are some of the areas with which syndicates can help?

Product profiles

Industry is well-used to the production and constant evolution of product profiles. They reflect the key elements any treatment must provide to meet a commercially-successful, meaningful medicine. However, it is often the case that product profiles

exist behind the walls of corporations and often only reflect one manifestation of disease or its impact upon the patient. Syndicates can take best practice from organisations such as the Medicines for Malaria Venture (MMV) where desired product profiles are refined by experts and published on behalf of the community. The ability provided to the syndicates to do this will allow them to think not just of the prime disease but also those elements often overlooked. For example, in Alzheimer's disease the syndicate can be enabled to publish a Patient Product Profile (PPP) for a range of symptoms including agitation, which is a key element of a patient's experience of disease, but often falls off the edge of the stage when the tier one journal, disease modifying A-lister troops on. These profiles may be arguable but will lead to awareness and calls to be made for companies with assets in that space to come forward. They may also drive consensus and be a true piece of pre-competitive work that all of industry can buy into.

The profiles will aid translational researchers to have a clearer idea of the types of asset that patients and industry want; to take the guesswork away from many of the groups who work on long-term programmes in the hope of industry engagement but, quite naturally, without the industry experience.

Visibility of pipeline and data

Essential disease understanding is today enabled by two things: access to patients and the assimilation of the basic research that is being done. In this the research charities can play a pivotal role for the syndicate. Not only do they have the trust of patients if they are needed for forming a new cohort, in many cases they already fund them. Consented access to real-world data in particular can provide syndicates with genuine, tradeable asset value from the start.

Charities also fund a massive volume of disease-focused basic research. In many cases, therefore, they have a broader perspective on the pipeline of targets, pre-clinical and clinical studies plus basic research activities than many of the public sector or industrial funding bodies. This can be harnessed within a syndicate to drive cross-discipline collaborations where they may not exist and line up a pipeline of potentially translatable assets. This pipelining is a typical tool of major industry, which enables clear decision-making and prioritisation, but its rigour is not always applied in non-industry settings. Imagine, therefore, if syndicates began to own and challenge pipelines on the basis of science, commercialisation potential and real world patient need. This could rebalance the efforts in favour of the patient but retain industrial focus and management.

Finding the air bubbles and removing them

The process of medicines R&D is a highly-complex pipework built up over years of trial, error and incremental change. The flows of drug and biomarker assets from target to Phase II can be tortuous. Often many assets are blocked behind bubbles caused by technology, process, access to skills, access to finance, regulation and patient recruitment. The syndicates will be highly attuned to the issues for their disease, working across multiple assets and assays running through the pipework towards their diseased patient. They are therefore the ideal real-world sensor for where to target 'de-gassing'. Any of these air bubbles can be approached through collaborative R&D or laser-focused resources.

For example, where the bubble is an inability to predict efficacy clearly because the assays are too simple to reflect disease biology – or not simple enough to pick winners – then the syndicate can gather help and use the solution to progress.

Where the problem is contractual, focused funding can supply the professional service resources which provide assets which will be useable across the syndicate.

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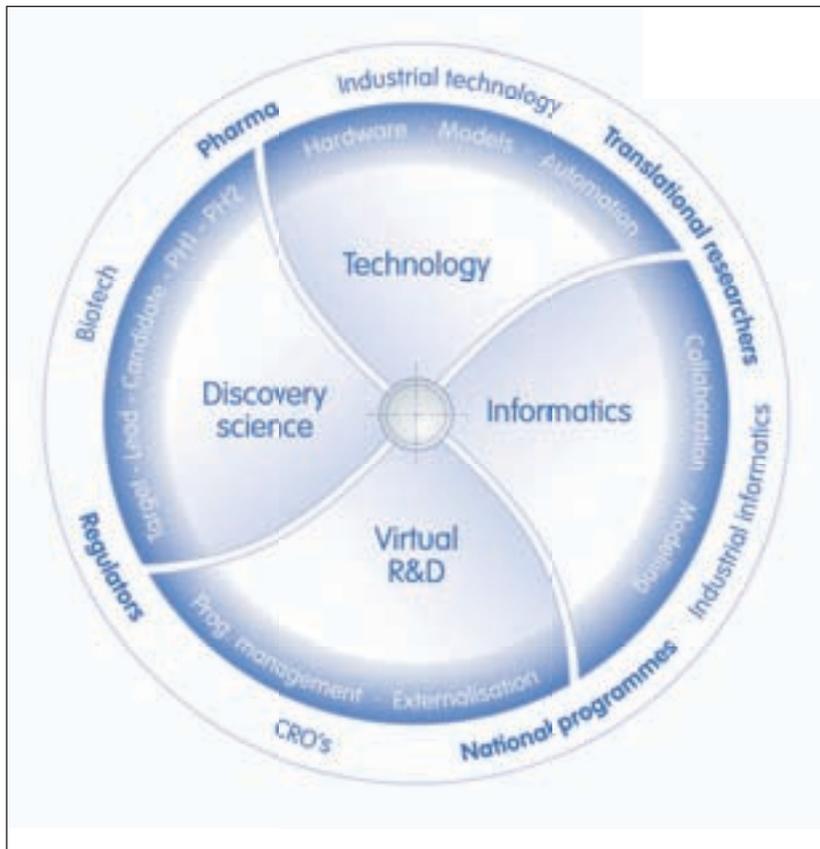
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Catapult activities and their natural industry partners

Where the problem is technological the syndicates and their agents can attract technology firms to address real-world problems. This is valuable to those firms themselves, as they often lack access to real-world opportunities to prove concepts either because SMEs do not have their own critical mass of R&D budgets or those that do (ie major pharma) do not share that problem.

Having multiple syndicates also helps in this regard. Where numerous groups hit the same problem the priority to address the barrier rises accordingly and not only can joint force be applied, external pressures can be brought to bear. This approach of ganging up on the problem is not new in other sectors, but where issues are siloed often people suffer in silence. Through active management of syndicates these problems will no longer be camouflaged but exposed and able to be managed.

Portfolios

Portfolios of assets lead to lower risk. That's a mathematical truth but it is also the case that single asset biotech's are focused. There is a clear difference of option as to which model prevails in a VC setting. However, the syndicate model thrives on

portfolio. As a structure designed to be long standing, there on behalf of the patient, it must help drive a portfolio of assets. These mixed portfolios can be driven efficiently through increasingly well-understood – and possibly shared – progression routes and where IP allows the learning from one asset can help that of another.

Fostering IP + SMEs

So what about the IP? The value that these syndicates can generate cannot just be about progression if it is to be sustainable in an IP-based industry. Running assets through syndicates should not mean everything has to be open book. There are excellent proposals for IP agreements published by Faster Cures and managing agents for the syndicates should be able to triage the IP to enable all participants to maintain rightful ownership of background and well-earned sharing of foreground.

While the model must reflect today's industry, IP fostering is now becoming a generation Y-compliant concept and there is much work to be done to advance medicines R&D into this era.

Syndicates must be able to give birth to SMEs and participate in their growth. Many of the assets validated by the syndicate, and at the right time in their development, may form the core of a new company. This should never be done too early, or in order to trade in equity before the company even gets going. These 'valuation crunches' can cripple a company at birth. The syndicate should be able to support and foster an idea until it knows there is a discrete product, asset of service that will help its patients.

Fast to patient packages

The syndicate may play an important advocacy and efficiency role in speeding up the time taken from idea to clinical PoC. Many regulatory bodies have to manage multiple separate conversations with multiple companies and or multiple assets through the same disease. Having a joined-up conversation with a disease-centred syndicate may enhance the efforts many of the regulators are currently making in their genuine wish to speed up patient access to safe candidate medicines. Being able to have such conversations may identify new packages of preclinical data that enable faster first-in-man through into Phase II. This is already being seen in the crisis area of Antimicrobial Resistance. With these new packages known, the syndicate can help ensure CROs are primed to perform these tests and thereby save time and resources for all.

New funding routes to fuel long term

The turbo that these syndicates represent accelerates and pushes more safe, efficacious patient-centred medicines towards the Phase III community. It is fuelled by money. The 6.5-year average for translation of idea to PoC is longer than the lifespan of many VC funds. This new long-term model therefore opens up new opportunities for how and by which means longer term funding can be sought. While the arguments rage across the VC community as to exactly how patient the capitalists should be, the focus of the syndicate should be on accessing the money targeted at the patients, by the patients and for the patients. Again, Faster Cures has proposed a venture philanthropy model which can be built upon. We believe that many more proven routes are open. The flexibility of a syndicate model, developed in a safe harbour, may effect even more opportunity to fuel the seeding and growth capital which companies need.

The pivotal role of CROs and industry consultants

The growth of the CRO sector over the last 10 years has been exponential. The shift from outsourced services to trusted IP generators has changed the balance of power and the dynamic options now open to the community. CROs will play a powerful role in enabling the work of syndicates. Through independent managed agents the syndicates and their members can access independent, best-in-class experiments and manage the data coming from them: sharing specialist techniques where they have them and also define best practice assay cascades where they do not. Strong relationships can be built with specialist CROs to provide further focused IP generation, technology proofs and fast-to-patient solutions.

The medicines discovery community has a wealth of senior level experience that has left pharma – particularly over recent years. This international brains trust and experience bank is tappable and usable to form *ad hoc* groups of specialists able to advise and direct syndicates without the need for permanent scientific advisory boards who may not have the depth (or bandwidth) across all aspects to handle the expansive needs of the portfolio.

Academia and industry: let Bartlet be Bartlet

In season one of *The West Wing* – possibly the most entertaining management training video ever created – fictional President Josiah Bartlet, Nobel prize-winning academic was trying to be someone

he was not, and was failing himself and those around him. In the end he was allowed to be himself and play to his strengths. So too must we recognise the strengths and weaknesses of the stakeholders around the medicines R&D table, and how to get the most from each. There are things that both academia and industry do exceptionally well.

Innovation and long-term, ‘never-say-die’ risk-taking are hallmarks of a vibrant academic community; rigorous decision-making and focus on the product are what have made the pharma industry the powerhouses which produce the world’s medicines.

There are examples where the interface between the two groups is good. Interestingly, these are often closely associated with key individuals, which reflects the fact that these activities require the rare ability to understand the needs and behaviours of others. There are, however, many examples where both groups would benefit from improved brokering. This could be in the form of better understanding of how product profiles and compound profiles match up, identifying the consensus for the ‘killer’ experiments which would enable industry to engage with an asset, or even to provide an independent performance of the pivotal validation experiments. The syndicate and its independent agents would be a natural environment for these activities to take place as they would combine sector experts, access to assets, industrialists and the patient voice.

MDC

The Medicines Discovery Catapult (MDC) is the UK’s new national centre for expertise in medicines discovery and early development. One of 11 Catapults in the UK was established by Innovate UK in 2016 to provide an applied R&D platform that enables stakeholders to collaborate around shared problems. The goal of the Catapult is to maximise the wealth and health of the community that seeks to discover and prove new therapies outside the cell and gene therapy arena. It is headquartered in Alderley Park, Cheshire, UK where it has lab, informatics, collaborative working and project externalisation facilities.

MDC provides scientific, process and informatics expertise that help partners develop new technologies, products, services and IP which make a difference. It works with charities, biotech, major pharma, CROs and other professional service providers as well as hardware and information technology providers, acting as a neutral broker and cross-domain expert.

MDC core assets diagram

The syndicate model is one core element of MDC's innovation in the medicines R&D. MDC will provide a framework for syndicates to form and act as managing agents to ensure smooth running of projects and the maximal confluence of charities, translational researchers, SMEs, focused pharma and technologists.

Summary

Not every innovation in medicines R&D needs to be technology-based. Many advances can and will be made by having the right stakeholders around the table. MDC's discovery syndicate model is designed to put patients at the beginning of discovery and enable them to influence the direction that industrialists and translational take. It is a model designed to develop sustainable portfolios of disease-focused assets and influence regulatory packages. Syndicates can also provide a magnet for SMEs, technologists, focused and innovative funds. Through development and expansion of these Discoverome syndicates with access to shared and best-in-class global resources, the entire community and the patients we will all be one day can be healthier and wealthier. **DDW**

Chris Molloy has more than 25 years' international executive and board experience across multiple areas of medicines discovery. He began his career in discovery biology at Glaxo and has delivered transformational change across research by implementing specialist automation and informatics systems. He moved into biotech as Chief Operating Officer of MerLion Pharmaceuticals in Singapore. During his tenure, MerLion raised significant international finance and advanced two novel antibacterials into clinical development. On returning to the UK in 2008, Chris became VP Corporate Development and Marketing at IDBS, a high-growth international software company focused on improving R&D and healthcare organisations through better access to data. This included the creation of the UK's first stratified medicine informatics platform, co-funded with Innovate UK. He was previously CEO of RSA, a senior-level global talent advisory firm specialising in life sciences. Chris has held many board and advisory roles and acts as CSO for KFLP Biotech LLP, a virtual drug discovery company focused on new treatments for HIV.