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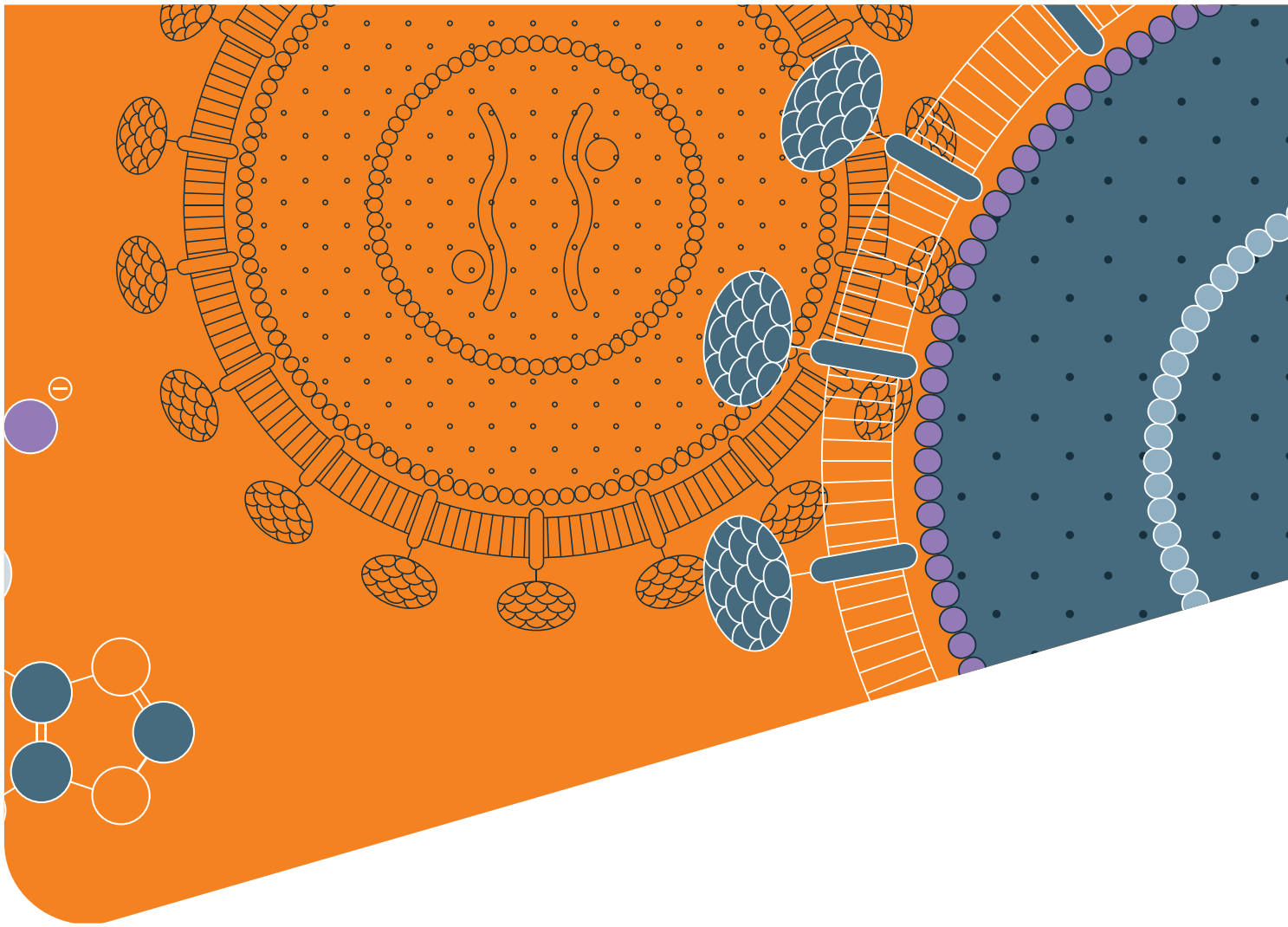

White Paper

EXPLORING THE DRUG DISCOVERY & DEVELOPMENT LIFECYCLE

ADVANCING DISCOVERY

Three case studies from across R&D

nature research

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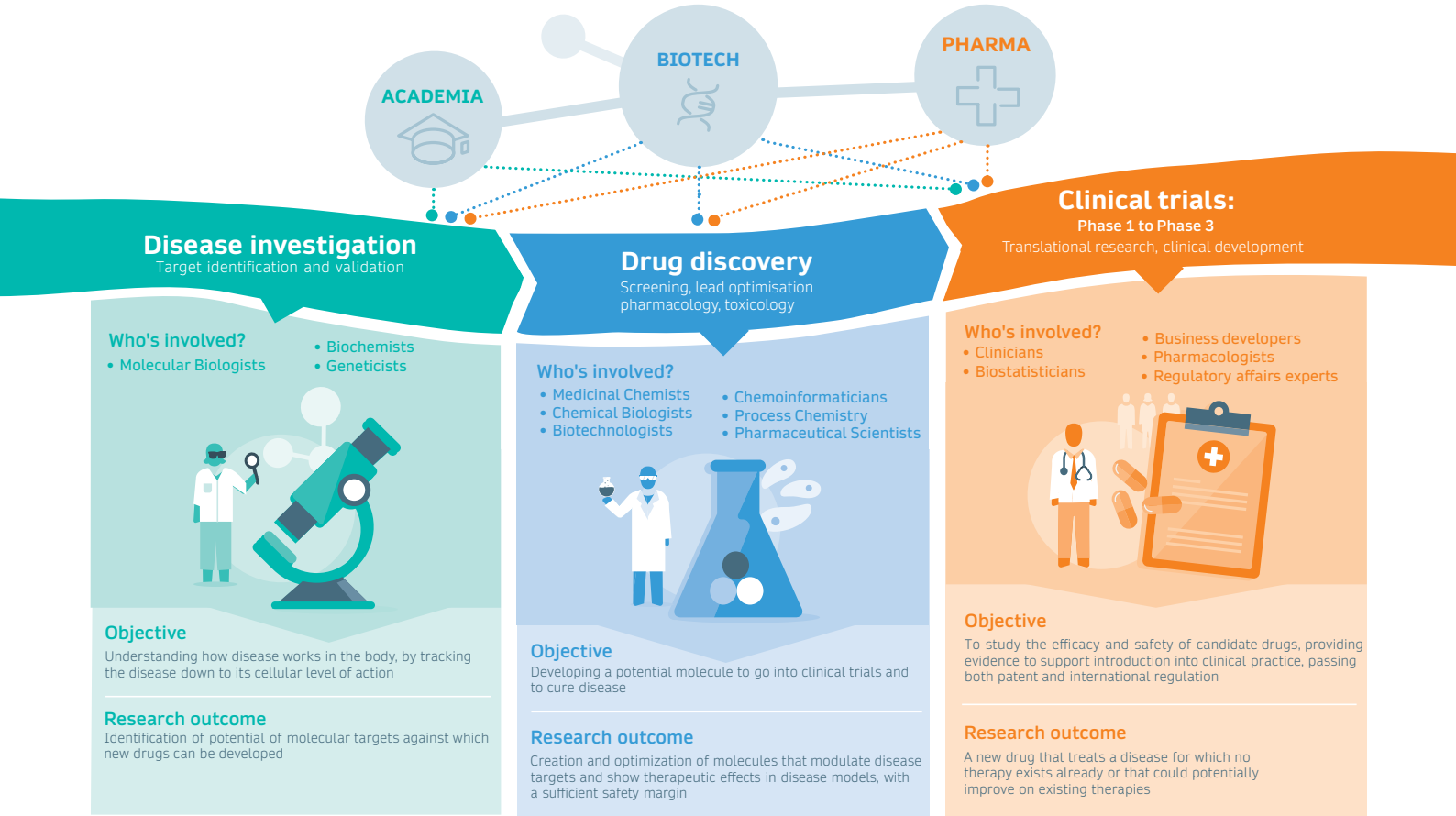
Contents

Introduction

Here we focus on three short case studies to give a snapshot of the current state of drug discovery and development. There have been many recent changes to the drug discovery lifecycle which include a more diverse research ecosystem, an increasing use of technology, analytics and modelling alongside a focus on patient-centred medicine, all of which are driving changes in scientific methodologies, working practices and results generation.

The case studies focus on different stages of the lifecycle and aim to explore how researchers are tackling some of the major challenges in drug development, and how new and updated approaches are changing drug discovery and development workflows.



The Drug Discovery lifecycle in overview

Drug Discovery and Development is one of the most important commercial scientific pipelines. This process by which scientists and clinicians deliver new efficacious drugs to market depends on scientists having the resources and methods to investigate disease and develop drug candidates. This is not just relevant for new therapeutic areas. It is important across therapeutic areas to deliver new drugs for existing conditions where serious challenges exist such as antibiotics, chemotherapy and treatments for neurodegenerative disorders.

The established process of drug discovery pipeline found in big pharma companies has been industry standard across organisations in drug discovery. The processes from identifying a disease target to an isolation of drug candidate, to taking a candidate molecule

through development and clinical trials and to approval and licencing for use in the clinic is one that is well documented. However, this structure is morphing as pharma continues to shift its model to accommodate changes driven by the ongoing impact of a number of major factors that have affected the industry over the last 10 years. From the patent cliff, late drug candidate failures, inefficiencies in research, research dead-ends and the high cost of bringing a successful drug to market, more efficient, creative research and development practices are now seen as essential to the discovery of better and more affordable drugs.

Scientific and industrial trends in drug discovery and development

Although big pharma is still central to the drug and healthcare industry, a multiplicity of factors is acting on the industry to drive a transition to a broader system of scientific discovery networks. This has generated a more diffuse and diverse research ecosystem made up of clinical research institutes, university spinouts, biotechs, contract research organisations (CROs), AI-led drug discovery start-ups and clinical trials specialists.

In these case studies, we will be looking at the growth of some of these factors as the increasing use of data science in drug discovery; leaner outsourced drug discovery and development and the move to higher levels of precision science and reproducibility from day one of the research. Finally, the paper looks at how a more patient-centred approach in drug development and in clinical setting has developed in pharma and biotech, and between researcher, clinician and the patient.

Several of these approaches covered have existed for a number of years as active topics in academic research and medical debate. They are finally moving to become both commercially viable and at the centre of patient drug therapy.

New approaches in drug discovery – case studies

David Wild: how upstream drug discovery is being transformed by data science

While traditional disease discovery is centred in the biology lab and focused on cellular, biochemical or genetic models, there are new approaches to target discovery and drug candidate prioritisation that are coming on stream. One of the most important is around data science and analysing the huge banks of existing research information and published data.

David Wild, an expert in chemoinformatics and data science at Indiana University, is using new data methods to look for disease targets and potential compounds. Using data tools he and his team have developed, they help researchers and pharma companies find a faster way of discovering a drug and bringing it to market.

“Research can use integrative data science, tools such as knowledge graphs to aid disease understanding and drug discovery.” David says. “There are now quite a number of small AI-driven pharma companies looking at solving some of the big pipeline problems using data science. Data science is forcing pharma, just like many other industries, to rethink their models. Early-stage biologists are tasked with finding target IDs which then feeds in to identifying compounds with potential, but the current pipeline isn’t working in a way that is sustainable long term when you look at the return on investment on research. The question is, can we find a different process that can make the drug discovery process sustainable?”

David uses a combination of data and AI to drive a process for early drug discovery different from the traditional biologist. Rather than returning to more basic biology research, he works with clinicians who are specialists in the target disease to take existing biological research and data patterns to shortlist potential compounds for a disease target that have potential. “Once we have identified a compound that might have potential,” David says “This moves over to wet lab testing, which is lab chemistry. That’s the fairly economic part of the process, unlike clinical trials that can cost on average $10 million.”

David Wild

Chemoinformatics and data science expert, Indiana University

David sees the strategy to transform drug discovery through the integration of large pools of data. "We are just starting to see the commercial impact of data science on the early stage drug discovery. One large pharma company recently employed 200 data scientists to build out their knowledge." This is a step change in terms of employment patterns and how the industry views data science and information analytics.

A recent paper in *Cell* showcased the first antibiotic to be identified by this technique by a team of MIT researchers. Using neural networks to investigate known molecules and previously published data, they were able to use a combination of AI and synthetic biology to find a completely new antibiotic. The research team thought this promised new opportunities in neurology and oncology, precisely the areas being investigated by David Wild's project.

A major source of untapped data is pharma companies with their vast quantities of internal data. First steps have been made by many in pharma to get all their data on a common platform or in a data lake, then to begin to map the content. Part of capitalising on this change will be a willingness for open sharing of early results to help speed discovery and stop unnecessary replication of research. This could take the form of a public pre-clinical and pre-competitive sharing of results. Then there is a second layer of data which exists: experimental, curated and structured and in public data sets such as ChEMBL, PubChem and PubMed.

Drawing on all pools of data, David and his team build out knowledge graphs of the most useful data, such as expert opinion; tools that give additional insights on disease markers and targets to medicinal chemists. Many big pharma companies such as Eli Lilly are putting a lot of investment into these approaches. For example, early work around Parkinson's disease discovery, such as the PRIDE project, uses Parkinson's medical experts to help to find new insights into the data with the potential for the discovery of new drugs. One radical side of this approach is that it not only uses clinical data, but also post-market release patient data, an example of real-world evidence feeding back into the research process.

"The question is, can we find a different process that can make the drug discovery process sustainable?."

Allan Jordan: Drug Discovery and early development: outsourced research focused on improved reproducibility, precision and the patient focused outcomes from the start

In the last 20 years, the drug discovery process focused on taking a large quantity of candidate compounds and testing them against the biological target. The approach was very common until recently and slowing of drugs coming through the pipeline has led to this approach being reviewed.

Allan Jordan is a medicinal chemist, and the Director of Oncology Drug Discovery at Sygnature Discovery, providing drug discovery services to big pharma and biotech companies. Understanding contract research is important as it's now a major part of the drug discovery and development ecosystem, with outsourced services from wet labs to clinical trials. Allan describes the work at the CRO supporting and driving drug discovery for both big pharma and biotechs, "I look exclusively at small molecules and at the cutting edge of small molecule drug discovery in oncology."

Outsourcing of 'wet' research is a big change from how pharma used to be run, "Especially for new organisations, there's a move away from investing in wet labs - the chemistry and bioscience labs that do the research and physical facilities by big pharma companies - to outsourcing this work to contract organisations. This structure often acts as an extension rather than replacement of a traditional research team. We become embedded in their processes." The range of research tasks that Allan and his team undertake spans from original concept development to hit-to-lead work, narrowing down candidate molecules, to early pre-clinical development.

"One of the things we see with drug discovery is that we need to look at more

Allan Jordan

Director of Oncology Drug Discovery
Sygnature Discovery

appropriate target identification. One of main actions is to take a robust look to see if there is a fully valid significance in the biological data. Reproducibility of results are very important in selection of the target. Often reproducibility of published results is poor."

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As Allan points out for a drug; "reproducibility on day one still has to be comparable to year five, this is much more stringent than basic biological research. Drug discovery is more hypothesis driven now. Ten years ago, we'd perhaps look at 1,000 targets and throw a million compounds at them, but we know this hasn't delivered in the way we expected. We now use a variety of hypotheses and screens to understand more about the targets and the best potential compounds to make drug candidate molecules to take forward into the pipeline. So, we use a combination of knowledge-based screens, virtual screening, chemoinformatics and high throughput screening to inform our selections and analysis."

Changes are also occurring to the type of molecule that can be a target. For example, in oncology, medicinal chemists are no longer just looking at a protein as a target molecule. Now a target can be DNA, RNA or a transcription factor. "Genetics was thought to be the magic bullet in solving cancer but it's proving to be more complex than that. Actual matching of drug to target is fine, but genetic plasticity gives rise new subclones with altered drug targets that exhibit resistance. Also, the coding region that generates these targets is only 20% of the genome, we know most of the other 80% is doing something else. This means changes at the genetic level may not be as dramatic or as universal as we think."

As with much of medicine, patient-centred approaches are becoming more critical in oncology. "The way we evaluate a drug target is changing," says Allan, "Oncology used to be considered a dirty therapeutic area with a lot of cytotoxic drugs. Now we see an increasing drive to understand combinations and better tolerated PK/PD (how the drug is taken into the body and metabolised) so it has a cleaner profile without overt or intolerable off-target side effects. Over the past 20 years, this has often been overlooked in the drive to find a cure or prolong life. The genetic angle is part of this, we can make drugs that are better for the patient. Patients, even if they know it will make them live longer, will refuse a drug if the side effects are too much. They would rather have 3 months with a decent quality of life than 6 to 9 months with none."

Despite what has often been reported in the press about the future of pharma and the drug pipelines, Allan believes the prospect of blockbuster drugs still exist and drugs will still be created that have wide and frequent usage. Many recent oncology drugs are finding wide applications after being approved and launched for clinical use.

Anna Pedret-Dunn: the changing face of drug development

A candidate drug begins its journey towards the clinic in the process known as drug development. Drugs that were promising in early discovery can subsequently fail in later stage clinical trials, demonstrating the importance of the drug development process in the delivery of safe and effective medicine.

Anna Pedret-Dunn, who trained as an analytical chemist, now works in drug development, within the field of Pharmacokinetics. Working in oncology, which is now a major focus for pharma, Anna's projects range from phase 1 to phase 3 clinical trials. For Anna, timescales in oncology development can run over several years. "Just to start the study, to get the first patient treated, can take six to nine months, The running of clinical trials involves large cross-functional teams, and dozens to hundreds of people involved to support the oversight of the study and the managing of the data collection which must be done following international guidelines such as Good Clinical Practice. Studies can run for years but typically they take a minimum of between 2 and 3 years. Pivotal oncology studies typically look at overall survival progression (measuring outcomes such as overall survival, or progression free-survival for example) and stabilising the disease.

Anna Pedret-Dunn

Medicinal chemist working in drug development

Anna describes how clinical trials are structured in 4 phases. “Phase I involves selecting the right dose and working out what is the maximum tolerated dose for patients, here patient safety is the prime consideration, if and how side effects can be controlled, and characterising pharmacokinetics. Phase II looks at how to get the right dose and delivery for the drug for particular indications with phase III (also called pivotal studies) looking at demonstrating efficacy, often against a known standard of care”.

Anna is currently supporting two Phase III trials. Pharmacokinetics is the study of the way the body affects the drug over time: how it is absorbed, metabolised, distributed and eliminated. Phase III trials can involve hundreds of patients, as Anna investigates how the compound behaves and what is causing the variability in effectiveness or side effects of the drug. Important sources of variability could be for example, how this could be related to gender differences or other differences between populations of patients from ethnic groups or external factors such as diet or medications having an impact.

“The emphasis always has to be on safety, and it has to be efficacious, otherwise it is unethical.”

Anna says, “Current practice has evolved to become much more patient-centred, so it is important that phenotypic and genotypic differences are taken into account. It’s important to define the patient population very carefully. For example, in a test for a compound with a positive reaction to the metastatic breast cancer hormone receptor, it is important to understand from the pre-clinical studies what population is likely to benefit more in the trial. For this we will draw on information from major oncology conferences such as the ones run by ASCO. Clinical study protocols for clinical trials aim to exclude anything that isn’t well understood or will be detrimental. Clinical trials are trying to answer a question, which is not only does a drug work, but what is the effect on the well-being of the patient?”

One of the major stages in drug development is getting approval by the regulatory agencies. Anna says, “The regulatory piece is hugely important. We have lots of conversations with the agencies. Prior to clinical trials, it is usually worth discussing with the agency regarding labels and approvals. Often the agencies have input into the design of the study, and we get feedback from regulatory agencies if they want to de-risk the programme. For example, the agency could be concerned about a sub-group from Phase II. There may some evidence to say that a subgroup is at a higher risk and that perhaps the dosage needs to be adjusted. We know the subgroup metabolises the compound differently – is it more effective or more toxic? The emphasis always has to be on safety, and it has to be efficacious, otherwise it is unethical.”

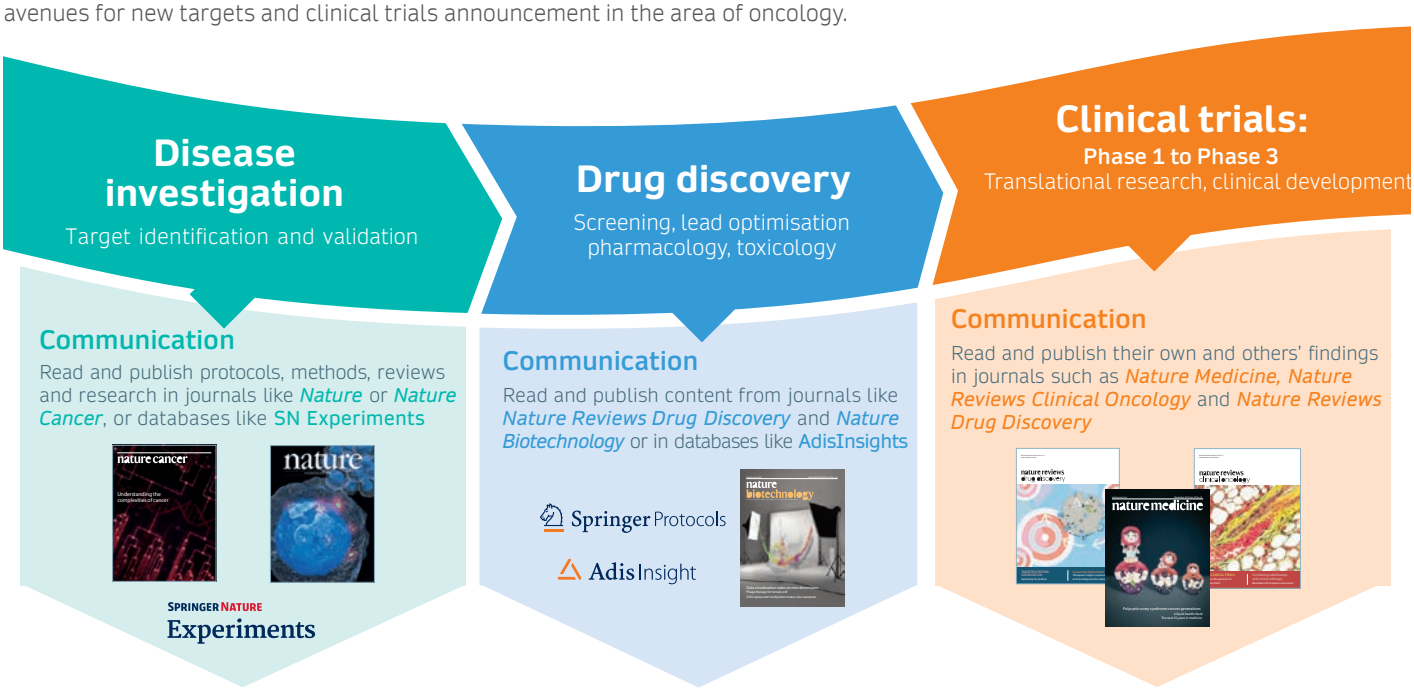
Publishing and pharma

Published research continues to be important to all three researchers in term of disseminating research but also a source for new ideas, information, potential targets and updates on therapies. David Wild continues to publish his research in chemoinformatics journals and his more specific work on algorithms for knowledge graphs in more specialist journals. He rates selective journals but also uses new open initiatives such as BioRxiv to get peer review feedback fast. David comments that in publishing research in pharma and data science, “It’s really important to stay above the noise and see the big trends. That’s where the selective journals are critical.”

While Allan Jordan’s team use published literature as sources for targets and basic biological findings, his work needs to see robustness in peer-reviewed literature with good levels of reproducibility. He is interested in continuous improvements in the robustness of science in even the highest impact biological studies, as his work needs reproducibility right from the very start. Pressure to publish and make an impact should not make a difference on how rigorous the results are. The need for high levels of reproducibility in drug discovery and being certain that the target is worthwhile pursuing, makes it essential for him and his medicinal chemistry team to take published targets through serious testing at early concept stages to ensure that the published results are reproducible and repeatable.

“It’s really important to stay above the noise and see the big trends. That’s where the selective journals are critical.”

Getting your results in front of the scientific community is as important to corporate researchers as it is to academics. For Anna Pedret, there is a big push to publish results, "We publish in very specialist areas often on the PK (pharmacokinetics) of a study. We may have already published the top-line study. In that case, we can't republish existing results again, which in the industry is called an encore. I've been in my current role about two and a half years, in terms of publishing, it takes about 1 year to get an abstract together and 18 months to 2 years to publish the results of an ongoing trial." The results of trials are often eagerly awaited by the medical, scientific and finance communities with conferences, as an example the ASCO conference is one of the major avenues for new targets and clinical trials announcement in the area of oncology.



In summary

Drug discovery is changing in response to the transformation of science through computing and data science. It is also undergoing an evolution in the understanding of disease and developing a more patient-centred response to disease and drug development. In specialism like oncology, which already are driven by precision medicine, the change in focus is helping clinicians deliver better individual therapies for patients.

Reproducibility and sensitive reuse and analysis of existing research information and data are becoming more central to the drug discovery process as the need to reduce late stage drug failures, research inefficiencies and dead ends, increasing efficacy and safety all become critical at earlier points in the discovery and development process. There is also cost to consider with average costs of bringing a successful drug to market in the billions, the need for a more creative and efficient process using the best of current and previous publishing research is a step in the right direction to getting more affordable drugs on to the market in a more timely fashion.

The pharma and biotech industry are now trying to solve some of the most complex problems in disease. Tackling cancer, neurodegenerative disorders, new antibiotics to target resistant bacteria are accelerated by new techniques and more flexible research methods to make drug discovery and development faster, more sophisticated and more patient centred.

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David Wild:

link.springer.com/article/10.1186/s13321-015-0089-z

link.springer.com/article/10.1186/1471-2105-12-256

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Allan Jordan

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Anna Pedret

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