Discovery Deals Perspectives: 2014 to 2019

Drug discovery deals have become a key feature of many pharma companies' transaction portfolios. In our Deal Watch annual reviews in previous years, discovery stage deals represented approximately 12-17% of all the transactions reviewed. These early stage deals are almost all licensing-based, however very occasionally there may be a joint venture formed or even a company acquisition.

Notable for the sometimes over enthusiastic reporting of headline biodollars, these deals typically comprise multiple programmes under which the parties collaborate to discover new drugs against a range of therapeutic targets. The initial collaboration is normally time limited, for example for several years, and the deal structure usually employs what can seem a complex arrangement of options under which rights can be granted to the licensee for predetermined fees (Box 1). Also often featured are options for the licensor to take part in development or commercialisation activities further down the line.

This article reviews discovery deals from 2014 to 2019 with a focus on the financials associated with this type of transaction, the most popular therapeutic areas and types of therapeutic entities involved, and the pharma companies most active in deal making at this early stage. The data sets used in this article focus on those transactions that were announced with financial information disclosed. Overall approximately 200 deals were analysed during the period 2014-2019.

A number of deals utilising artificial intelligence (AI) approaches to drug discovery have also been reviewed and these will be covered in a separate section of this article.

Originally published in the PLG Business Development and Licensing Journal, Issue 29, January 2020

Box 1: Examples of options employed in discovery deals

Licensee's options:	Licensor's options:
• To take an exclusive licence to each drug candidate developed under the collaboration • To add further targets or programmes • To add further therapeutic areas or indications • To extend the collaboration timeframe • To acquire the licensor • To acquire a specified programme or asset	• To share clinical development costs for a profit:loss share arrangement or higher royalties • To co-promote a product in a specific territory • To retain commercialisation rights to the licensed product in a specific territory • To lead development to a predefined stage, e.g. in a specific therapeutic area

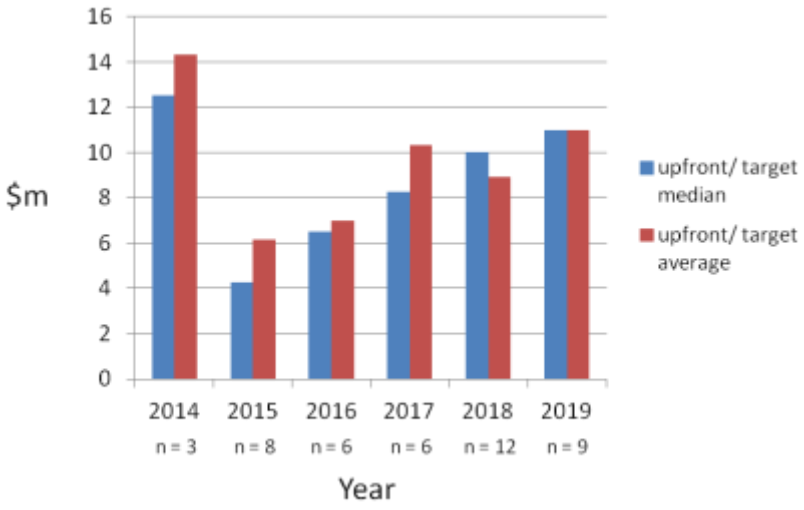
Financials - what do the biodollars actually mean?

There have certainly been many eye catching press releases and news articles for drug discovery deals touting multi-billion headline values. However, for a licensor to achieve such payments, it is assumed that all the discovery programmes within the deal will be successful and result in approved products. Also discovery deal financials are very back-loaded so the bulk of the milestone payments may only be paid later in development and after a product is on the market in the form of sales milestones.

A more meaningful approach to establish the value of a discovery deal is to assess how much is paid upfront, which is typically the only non-contingent payment, and to review the financials on a per programme or target basis. Not every deal press release contains all the relevant financial data to reveal the full picture so this section focuses on those transactions where the details are provided or where there is sufficient information to allow estimates to be made.

Figure 1 shows the median and average upfront payments adjusted per target or programme for discovery deals by year for the period 2014 to 2019. Figure 2 shows the median and average values for overall payments per target or programme for the same period.

Figure 1: Upfront payments on a per target or programme basis*

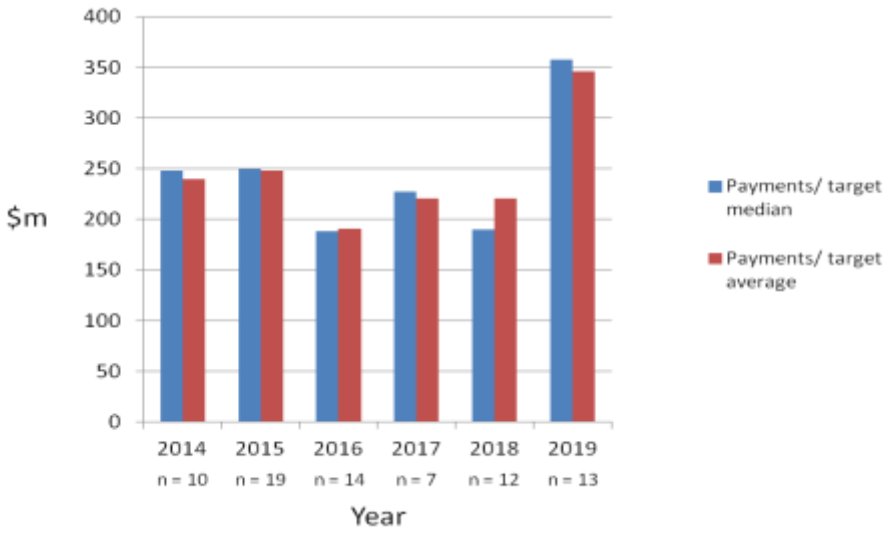


*Based on figures quoted or estimated from public information

Overall there appears to be an upward trend in upfront payments per programme from 2015 to 2019 (median: $4.3m in 2015 to $11m in 2019; average: $6.2m in 2015 to $11m in 2019). In 2014 upfront payments appear to be more generous (median: $12.5m; average: $14.3m), although it is acknowledged that this data set is based on only three deals.

The picture for financials per programme (Figure 2) is less consistent with no obvious trends between 2014 and 2018 but with an increase in these payments in 2019 (median: $250m in 2015 to $358m in 2019; average: $248m in 2015 to $346m in 2019).

Figure 2: Payments on a per target or programme basis*



* Based on figures quoted or estimated from public information

Of course, every deal is different and licensees may be prepared to pay more to access certain discovery platforms. In addition to upfront payments, milestones and royalties (see later), R&D funding and equity investments are also a feature of many deals but information on these aspects is not always disclosed. Some examples of discovery stage deals are illustrated in Table 1.

As mentioned above these early stage deals are mostly back-loaded. Review of the examples in Table 1 on a per programme basis (where it can be estimated), shows that the upfronts represent a small proportion of the overall payments, ranging from just over 1% to approximately 6%.

Table 1: Examples of discovery stage deals during the period 2014-2019

Licensor/ Licensee (date)	Technology/ Platform	Field	Comments/ Financials
Nurix Therapeutics/ Gilead (2019)	Drugs that control ubiquitin E3 ligase to induce degradation of specified drug targets; up to 5 targets	Oncology, other therapeutic areas	Multi-year collaboration; upfront $45m ($9m/ target) + up to approx $2.3bn ($460m/ target) in total additional payments, as well as up to low double-digit tiered royalties
Dicerna/ Novo Nordisk (2019)	GalXC™ RNAi platform technology for >30 liver cell targets	Liver-related cardio-metabolic diseases, e.g. chronic liver disease, NASH, type 2 diabetes, obesity, rare diseases	Upfront $175m, $50m equity investment in Dicerna; $25m annually during each of the first 3 years of the collaboration; up to $358m per target in milestones, plus tiered mid single-digit to mid-teens royalties
Kymera/ Vertex (2019)	Small molecule protein degraders against multiple targets - 6 programmes	nd	4 year R&D collaboration; $70m upfront ($11.7m/ programme) including equity; $1bn in milestones ($167m/ programme) for up to 6 programmes; tiered royalties
Zymeworks/ LEO Pharma (2018)	Antibodies to develop bispecific therapeutics targeting cytokine-receptor pathways	Dermatology, inflammation, autoimmunity	Up to $236m in upfront and milestone payments for the first therapeutic candidate, and up to $244m for the second, plus research funding payments and royalties
Tango Therapeutics/ Gilead (2018)	Functional genomics-based discovery platform - 5 targets	Immuno-oncology	Multi-year collaboration; upfront $50m ($10m/ programme) + approx $1.7bn in milestones ($340m/ programme); up to low double-digit tiered royalties
CureVac/ Lilly (2017)	RNActive technology for up to 5 potential cancer vaccine products	Immuno-oncology	Upfront $50m ($10m/ programme) + ~$53.1m equity investment; $1.7bn ($340m/ programme) in milestones, plus tiered royalties
Bicycle Therapeutics/ Bioverativ (2017)	Bicyclic peptides (Bicycle®) - 2 programmes	Rare blood disorders: haemophilia and sickle cell disease	$10m upfront ($5m/ programme), $4.2m near-term R&D funding, $410m in milestones ($205m/ programme); tiered single to low double-digit royalties
*Nuevolution/ Amgen (2016)	Chemetics DNA encoded screening platform for multiple targets	Oncology, neuroscience	Up to $410m in milestones/ per target, tiered royalties
Blueprint Medicines/ Roche (2016)	Up to 5 small molecule therapeutics targeting kinases for cancer immunotherapy	Immuno-oncology	Upfront $45m ($9m/ programme), **$965m in milestones ($193/ programme), research funding; low double-digit to high-teens royalties
BioNTech/ Sanofi (2015)	mRNA therapeutics for up to 5 cancer targets	Immuno-oncology	Multi-year collaboration; $60m upfront ($12m/ target); $300m milestones/ target; tiered royalties up to double digits
Heptares/ Pfizer (2015)	New therapeutics against up to 10 GPCR targets	Multiple therapeutic areas	Upfront undisclosed, $189m/ target in milestones, $33m equity, tiered royalties
Proteostasis Therapeutics/ Astellas (2014)	Screen for drug candidates that modulate the Unfolded Protein Response (UPR)	Metabolic/ orphan diseases	Upfront undisclosed; $400m/ programme in milestones, R&D funding and equity investment, tiered royalties
Immunocore/ AstraZeneca (2014)	Immune Mobilising Monoclonal T-Cell Receptor Against Cancer (ImmTAC) technology	Immuno-oncology	Upfront $20m/ programme + up to $300m in milestones / programme, tiered royalties

*Amgen acquired its partner Nuevolution in 2019 for $167m
** Of which ~$215m ($43m/ programme) is for option fees and milestones for research, preclinical and clinical development events
NASH, non-alcoholic steatohepatitis GPCR G, protein-coupled receptor nd: not disclosed

It is quite rare for press releases to provide information on a breakdown of actual milestones for specific events but some companies do announce when they have received a milestone payment. Valuable insights on milestones can also be made by reviewing companies' SEC filings. Some recent examples of milestones received are summarised in Table 2.

Table 2: Examples of early milestone events and payments for discovery deals

Partners	Milestone event	$m
Sosei Heptares/ Genentech	Nomination of a new G protein-coupled receptor (GPCR) disease target	3
Ionis Pharmaceuticals/ Biogen	Designation of a new target to advance for a neurological disease	7.5
Zymeworks/ Celgene	Selection of a lead oncology candidate - licence option exercise	7.5
Nuevolution/ Almirall	Completion of evaluation of preclinical safety parameters of RORγt inhibition to de-risk the programme prior to human testing	1.1
Five Prime Therapeutics/ GSK	Exercise of option to license IP related to a respiratory disease target	1.5
Zymeworks/ Merck & Co	Merck's completion of a late-stage preclinical study for a bispecific antibody candidate	2
Sosei Heptares/Pfizer	Nomination of the first preclinical small molecule drug for clinical advancement	3
Zymeworks/ Lilly	IND submission for an immuno-oncology bispecific antibody	8
Five Prime Therapeutics/ BMS	Filing of an IND for an antibody discovered under the collaboration	5

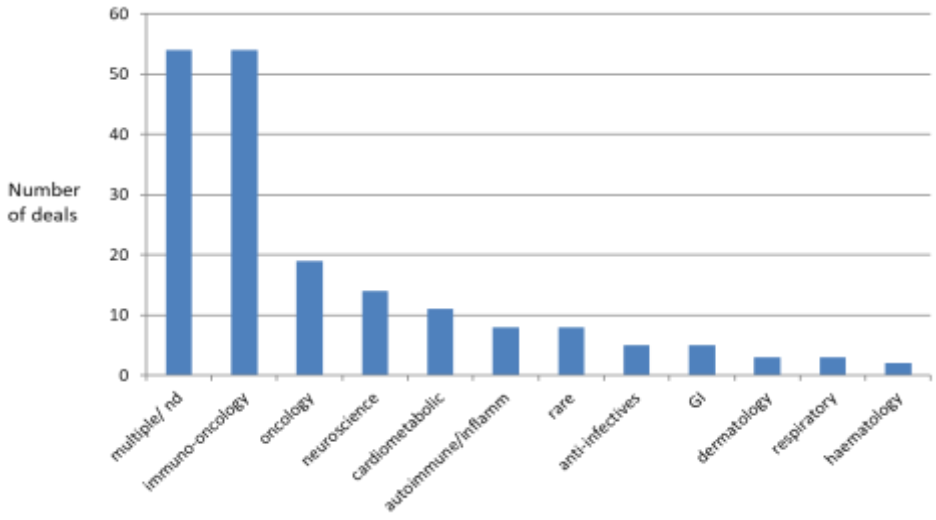
Source: Company press releases and SEC filings

Occasionally public announcements for discovery deals separate the development, clinical and regulatory milestones from the sales milestones. Examples of this include the 2016 collaboration between Nuevolution and Almirall for small molecule RoRgt inhibitors for dermatology indications. This deal had a headline value of approximately $479m; the milestones comprised $182m for development and regulatory events and $285m for tiered commercial sales milestones. Similarly, in the 2018 collaboration and option deal Incyte entered into to access Syros Pharmaceuticals' gene control platform for seven oncology targets, the per product payments were $50m in development and regulatory milestones and $65m in sales milestones. More recently in the collaboration between Exicure and Allergan to use Exicure's spherical nucleic acid (SNA™) technology to discover novel treatments for hair loss disorders, milestones per programme were $97.5m for development and regulatory events and $265m in commercial milestones.

In these deals, the majority of the milestones are dependent not only on a product reaching the market but most likely on the magnitude of sales achieved, underscoring the back-loaded structure of these transactions.

Actual royalty rates are very rarely disclosed in public announcements. Most discovery stage deals have tiered royalty rates with the range covering low- to mid-single digit up to low-double digit or mid-teens percentages.

Figure 3: Top 12 therapeutic areas for discovery deals: 2014-2019



Therapeutic areas

Figure 3 illustrates the top 12 therapeutic areas for discovery deals. This is consistent with observations in our Annual Deal Watch reviews in previous years where immuno-oncology/ oncology and CNS/ neurosciences were the top areas for deals at all development stages. By their very nature discovery deals can cover more than one therapeutic area and frequently the therapeutic areas of interest are not disclosed.

Immuno-oncology deals peaked in 2015 and 2016 and represented more than half of the discovery transactions during that period. Some of the deals targeting multiple therapeutic areas also covered immuno-oncology in those years. The indications that were disclosed in the neuroscience area included neurodegenerative diseases and schizophrenia, and in the cardiometabolic area the most popular indication appeared to be NASH.

Therapeutic entities - which are most in vogue?

The "old days" when small molecules were the only option in the pharmaceutical industry are long gone. Having said that most of the discovery deals in the six years reviewed were for small molecule therapeutics, with slightly fewer for antibody and other protein-based therapies (Figure 4a). Cell-based therapies (e.g. CAR T-cell immunotherapies) and nucleic acids (e.g. RNAi, mRNA) are also increasingly a focus. The number of deals focused on antibody and protein therapeutics dropped in 2019 compared to 2014 (Figure 4b) but cell-based therapies are on the rise; there was a peak in cell therapy deals in 2015. The number of nucleic acid-based discovery deals over the period was reasonably consistent from 2015 with three or four per year.

Figure 4a: Deals by therapeutic entity: 2014 - 2019

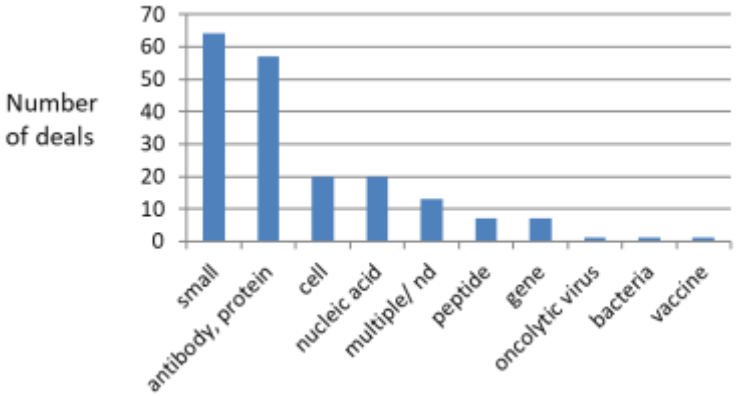
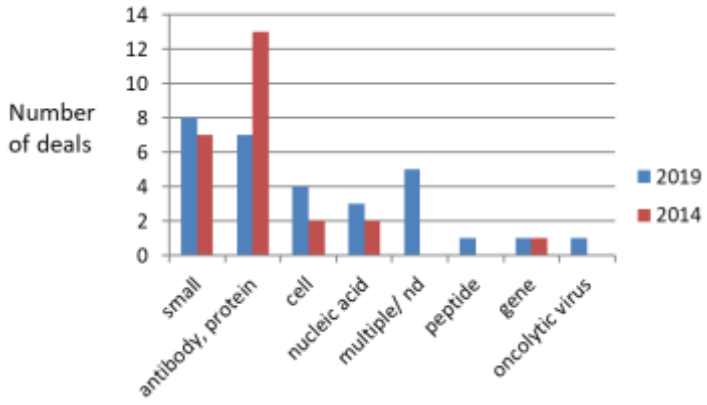


Figure 4b: Deals by therapeutic entity: 2019 vs 2014



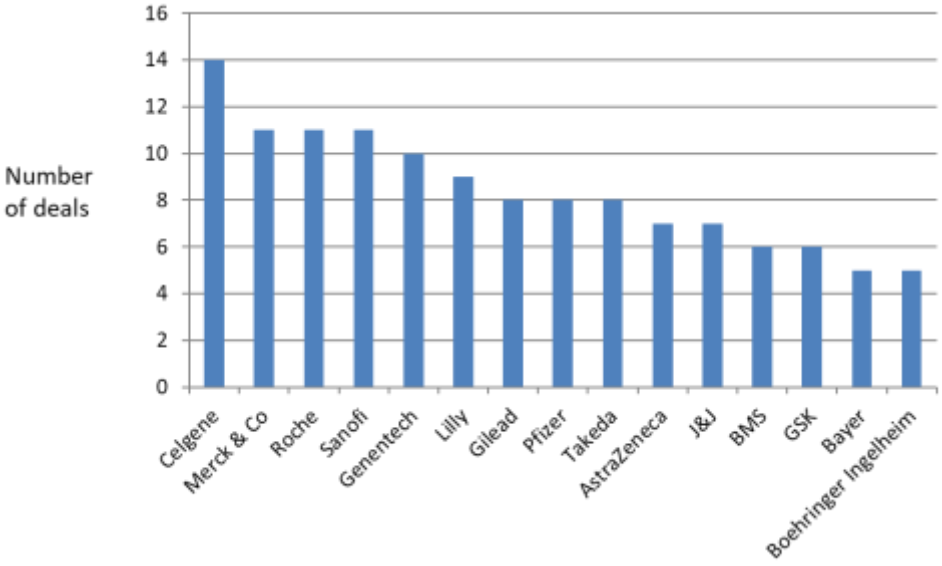
Most active pharma companies

Celgene was the busiest of the pharma companies doing discovery deals during the period (Figure 5). In our Deal Watch reviews from previous years Celgene always featured in the top 20 most active transactional companies (i.e. deals at all stages) and was noted for some of its creative deal structures. However, if Roche and Genentech are combined their 21 deals make them by far the most active in the discovery deal area.

Other major pharma that have a consistently busy deal track record feature in the top 15 in Figure 5. While companies such as AstraZeneca, J&J and BMS have been amongst the top ten deal makers at all stages in previous years, they have not been quite as active in the discovery space as some of the other pharma. However, with BMS completing its acquisition of Celgene in November 2019, this would move the combined company towards the top position.

It is apparent in drug discovery partnerships that a good relationship can bring further collaborations. There are many examples in which a pharma company and biotech have entered into a new partnership, for example in a different therapeutic area, or expanded an existing collaboration. It is also evident that biotech companies with a compelling discovery technology or platform can attract multiple collaborations with different pharma. For example, in 2019 Skyhawk Therapeutics entered into collaborations with Biogen, Merck & Co, Genentech, Takeda and Celgene to discover drugs based on its SkySTAR™ technology, which uses RNA-binding small molecules to selectively modify RNA splicing.

Figure 5: Top 15 pharma discovery deal makers: 2014-2019*



*Numbers based on deals which included some financial terms

AI - a brief mention

Artificial intelligence (AI) is one of the hot topics at the moment. The potential for AI in the pharmaceutical and healthcare industries is far reaching and beyond the scope of this article. However one area relevant to this discussion is the use of AI for drug discovery. Many companies have been set up to develop AI approaches to discover new drug candidates. One potential advantage is that novel candidates can be generated in a fraction of the time required for traditional methods. A number of large pharma have already set up collaborations in the AI area. While the majority of AI drug discovery partnerships announced provide no financial details, there are a few exceptions and some of these are included in Table 3.

Table 3: Examples of AI drug discovery deals

Licensor/ Licensee (date)	Deal type	Financials
Exscientia/ Roche (2019)	AI drug discovery collaboration to design preclinical drug candidates	$67m in upfront, R&D funding, preclinical, development, commercial milestones; tiered royalties
Exscientia/ Celgene (2019)	3 year AI drug discovery collaboration for small molecules covering 3 therapeutic programmes in oncology and autoimmunity	$25m upfront + clinical, regulatory and commercial milestones; tiered royalties
Insitro/ Gilead (2019)	3 year collaboration to create NASH disease models and discover up to 5 targets for metabolic disease	Upfront $15m ($3m/ target) + additional near-term milestones up to $35m ($7m/ target); up to $200m for preclinical, development, regulatory and commercial milestones for each target; up to low double-digit tiered royalties
Atomwise/ Lilly (2019)	AI drug discovery for up to 10 drug targets	Up to $560m ($56m/ target); up to $1m/ target in discovery milestones
Atomwise/ Hansoh Pharmaceutical Group (2019)	AI small molecule drug discovery against up to 11 target proteins, multiple therapeutic areas	Up to *$1.5bn ($136m/ target); undisclosed technology access fees, option exercise fees, royalties, and income based on sublicensing or sale of assets created under the collaboration
Atomwise/ Charles River Labs (2019)	Strategic alliance - AI technology to predict how well a small molecule will bind to a target protein of interest	≥$2.4bn* in potential royalties for Atomwise; Charles River to pay technology access fees, non-clinical milestones plus royalties from clients
Prometheus Biosciences/ Takeda (2019)	Identification/ validation of 3 unique IBD drug targets + development and commercialisation of companion diagnostics	Undisclosed upfront, up to $420m in development, regulatory, and commercial milestones ($140m/ target); royalties nd
Exscientia/ Sanofi (2017)	Strategic research collaboration, licence, option; AI-driven drug discovery for bispecific small molecules for metabolic disease targets	$277m in non-clinical, clinical and sales milestones; R&D funding; upfront nd
Exscientia/ GSK (2017)	AI preclinical discovery collaboration for up to 10 targets across multiple therapeutic areas	$42m ($4.2m/ target) in lead and preclinical candidate milestones + R&D funding

*According to the Atomwise press releases these financials are based on "calculations using historical industry average lifetime revenues for small molecule drugs". Inclusion of potential royalties, sub-licensing revenue and income from asset sales in a headline value is a very unusual approach to disclosing financials and some commentators might consider it misleading compared to the way other companies report deal financials.

Overall the per target payments under the AI-driven discovery deals in Table 3 appear to be on the low side compared to the traditional approaches to drug discovery. This may be a reflection of the as yet unproven nature of this methodology. Although they have not divulged the financials involved, there are many other collaborative partnerships ongoing in AI drug discovery with a wide range of companies. Time will tell if AI technologies are to become a major feature of the drug discovery process.

Conclusions

The challenge in drafting press releases for discovery deals is that while the licensor wants to illustrate the value of its assets and technology, the licensee is keen to be discreet about the financial terms and its deal structures to ensure it maintains any competitive advantage. From the information that is available it appears that there has been a gradual increase in discovery deal values from 2014 to 2019. This trend is expected to continue as the pharma companies' search for new therapies becomes more and more difficult. The main therapeutic areas of interest have not changed and small molecules and antibody-based and protein therapies are still the most popular, however there is increasing interest in cell therapy and nucleic acid-based projects.

Whether AI will make the discovery of new therapeutics easier or quicker remains to be seen. AI may be having a disruptive effect on the development of new products in other high technology industries but it has yet to be established in the pharmaceutical industry.

Jill Ogden

Jill Ogden has over 30 years of commercial and R&D experience in the biopharmaceuticals and healthcare industries and provides our biologics, early stage deals and platform technologies expertise. She has worked for a number of mid-caps and biotech companies, both public and private. Jill has led and been involved in a wide range of product and technology deals, including corporate M&A.

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