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Accelerating Drug Discovery Through Innovative Partnerships



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Genomics plays a vital role in identifying which gene is associated with a specific disease. A gene called CNOT1 is for example known for its effect on brain development and for impairing memory and learning.⁷ Despite the great promise genomics provides in understanding the disease, genes are not the best drug targets. Luckily, each gene usually codes for only a small set of proteins, which are promising drug targets. Currently, only 10 % of human proteins are known to be “druggable,” or likely to be a useful drug target.¹ The most common drug targets of currently marketed drugs include G protein-coupled receptors (GPCR; target of 50 % of drugs), enzymes (especially protein kinases, proteases, esterases, and phosphatases), ion channels, nuclear hormone receptors, structural proteins such as tubulin, membrane transport proteins and nucleic acids.



Discovery Challenges and Trends

On average, a drug takes 12-15 years from concept to patients. Preclinical development, which takes four to six years, includes identifying a molecule via extensive preclinical testing and process optimization to prepare for a phase 1 clinical test. Out of five thousand compounds tested, approximately five will appear promising enough to take the molecule forward to file an IND.² A hit can be identified by high throughput screening (HTS), focussed library screening, in-silico virtual screening, DNA encoded library screen, or smart design based on binding pockets and natural ligand interactions. When a real hit is found, it is most likely to be refined to increase its binding affinity or change its pharmacological properties. The probability for effectiveness can be enhanced by applying the Lipinski rule of five. Lead optimization aims to synthesis lead compounds, new analogs with improved potency, selectivity, and metabolic stability. During this process, thousands of molecules are being prepared by the medicinal chemists and chosen based on their fitment for the next step of drug discovery. Lead optimization can be accomplished by modifying the hit structure using structure-activity relationship (SAR) and structure-based design. Once the NCE is identified, the drug development process begins with preclinical pharmacology (animal studies) and clinical pharmacology (human studies). During the preclinical studies, the drug is subjected to extensive pharmacological studies on animal models (both in-vitro and in-vivo) to analyze the toxicity profile, therapeutic index, and pharmacokinetics. Before entering into the market, drug candidates are extensively examined to assess their efficacy and toxicity in humans.³



An Overview of Kinases and PROTAC:

Kinases have been intensively investigated as drug targets for the past 30 years, with 38 kinase inhibitors approved to date. These drugs are predominantly multitargeted receptor tyrosine kinase (RTK) inhibitors approved to treat cancer, such as imatinib. In addition to cancer, deregulation of kinase function plays an important role in immunological, inflammatory, degenerative, metabolic, cardiovascular, and infectious diseases. The established druggability and the clinical safety profile of approved kinase inhibitors make kinases attractive targets.

A novel and powerful strategy, PROteolysis TArgeting Chimeras (PROTACs), has attracted significant attention both from academia and industry for discovering new types of therapeutic agents relying on their unique characteristic of degrading target proteins instead of inhibiting them. Therefore, PROTACs are particularly sensitive to drug-resistant targets, commonly caused by exposure to high concentrations of small molecule inhibitors. Since PROTACs act catalytically, the scope of proteins used for treating diseases has been expanded by PROTACs. Besides, PROTACs exhibit better selectivity when compared to classic inhibitors. More importantly, PROTACs can affect the nonenzymatic functions of proteins, facilitating the control of protein functions that are not easily achieved by traditional small-molecule therapeutics. With their speed and reversibility, PROTACs present a chemical knockdown approach. More target binders and more E3 ligases applicable in the development of PROTACs are waiting for exploration.⁴

Nat Rev Drug Discov. 2018 May;17(5):353-377.

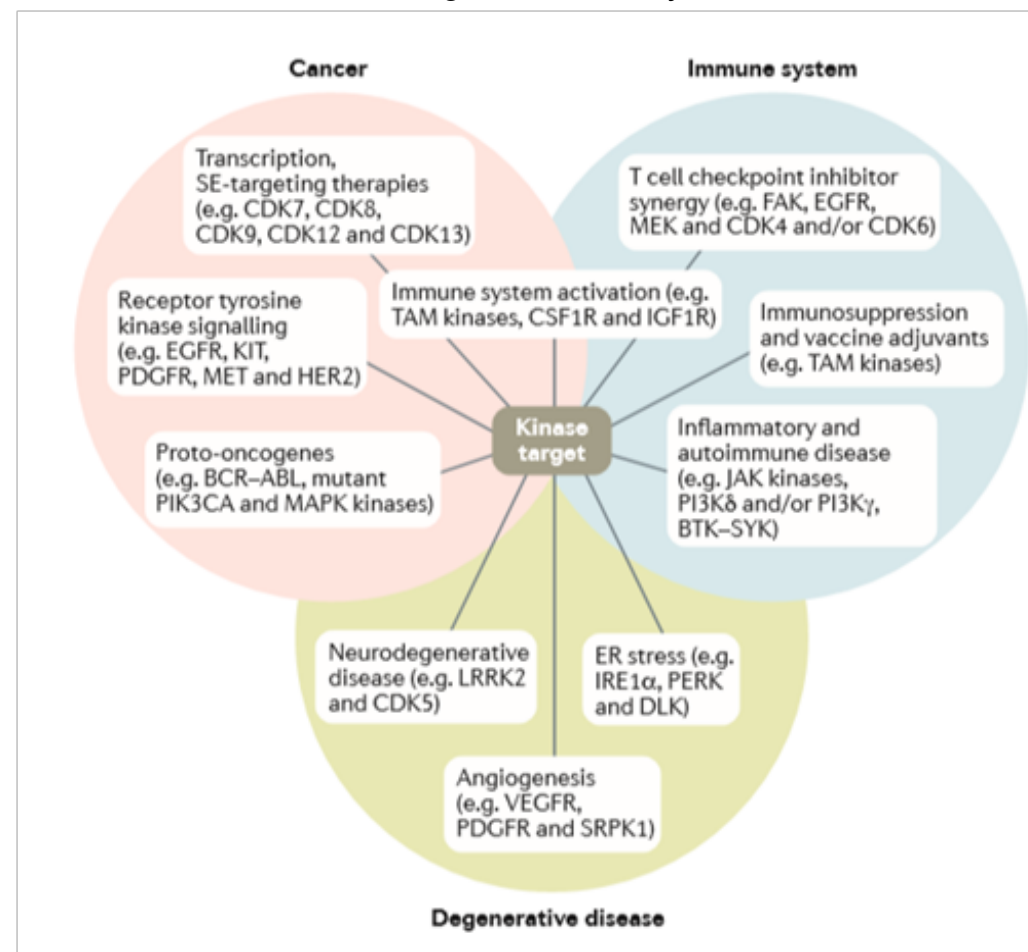


Figure 1 | Kinase inhibitors in diverse biological processes and new therapeutic areas.

Novel Drug Targets Approved in 2018 and 2019 by the US FDA

Among recent drug approvals, we see that the US FDA increasingly approves new drugs with mechanistic novelties. In 2018, six of the novel drug targets emerged from already established protein families: kinases (two), G protein-coupled receptors (one), enzymes (two), and transporters (one). Four monoclonal antibody (mAb)-based drugs target secreted proteins (a growth factor, a coagulation factor, a cytokine, and a neurotransmitter peptide). Two proteins are of viral origin. From a therapeutic area perspective, oncology, hematological disorders (beyond cancer), and infectious diseases each gained three novel targets. In the oncology area, larotrectinib, the first drug targeting tropomyosin receptor kinases, also represented the first approval of a developed drug specifically for a tumor-agnostic indication. Caplacizumab, which targets the von Willebrand factor to treat acquired thrombotic thrombocytopenic purpura, is the first nanobody to be approved, and ibalizumab, a mAb that targets the CD4 co-receptor used by HIV to enter T cells, is the first biologic to be approved for HIV infections. There were also particularly notable advances in the central nervous system disorders, with the approval of the first anti-migraine therapies with a novel MoA — targeting calcitonin-gene-related peptide (CGRP) signaling — since the 1990s. Two mAb drugs, fremanezumab and galcanezumab, target CGRP, whereas erenumab targets the CGRP receptor and is also a pioneering approval of a GPCR-targeted mAb.⁵

In 2019, four targets were in the well-established transporter class, including two transporters in the SLC superfamily, SLC9A3, and SLC5A1. There are also three RNA targets, reflecting the strengthening clinical validation of oligonucleotide-based therapeutic platforms. Different classes of oligonucleotides can degrade the target RNA — as with volanesorsen, an antisense oligonucleotide that degrades apolipoprotein CIII (apo CIII) mRNA, and givosiran, a small interfering RNA (siRNA) that degrades the mRNA for 5-aminolevulinate synthase — or restore protein function through the promotion of exon skipping, as with golodirsen, which binds to exon 53 of dystrophin pre-mRNA. From a platform perspective, two targets are for antibody-drug conjugates, enfortumab/vedotin and polatuzumab/vedotin, which enable the highly toxic, microtubule-disrupting agent vedotin to be delivered to cancer cells that express nectin 4 or CD79B, respectively. From a therapeutic standpoint, nine of the novel MoA targets address rare diseases. Five of these targets are genetic disorders with hematological manifestations, including two new targets for sickle cell disease: the hemoglobin subunit- α and P-selectin.⁶

How Partnerships can Accelerate Drug Discovery and Extend Capacities

Despite scientific innovation, the need to understand the biology, identification of novel targets and the mechanism of action towards diseases is increasing day-by-day. Institutions, pharma and biotech companies are under extreme pressure to discovering new treatments to meet unmet patients' needs while balancing R&D costs, timelines, and success rates.

Understanding the pain points in discovering a molecule, Aurigene Pharmaceutical Services is ideally positioned to meet the changing needs of today's drug discovery challenges. With its state-of-the-art infrastructure and hands-on experiences, Aurigene Pharmaceutical Services accelerate your discovery program from early discovery (Hit, hit to lead) to late discovery (lead optimization) to preclinical – IND (candidate nomination and DS-DP support). Our discovery services combine computational chemistry, protein sciences, medicinal chemistry, analytical chemistry, biochemistry, cell and molecular biology, ADME – PK, pharmacology, pharmaceutical development, safety, human PK predictions and toxicology, but are also able to provide standalone services.

At Aurigene Pharmaceutical Services, the [medicinal chemistry](#) team can handle the discovery of small molecules and peptides from mg- to g-scales. Within small molecules, we handle reactions between -78 °C to +250 °C, air and moisture sensitive reactions, chiral chemistry, and various organometallic chemistry. Using a microwave-assisted peptide synthesizer, our experts bring down the turn-around time for synthesizing peptides. More than 250 crystal structures were characterized by our protein sciences experts. Our [DMPK services](#) include assessing physicochemical and druggable properties, PK/PD and IND/ ANDA studies in a regulated environment. Our [in-vivo pharmacology](#) team supports the profiling of compounds to multiple therapeutic areas includes oncology, metabolic disorder, pain and inflammation, infective diseases, and others. Aurigene Pharmaceutical services successfully handled numerous drug targets, including kinases, proteases, phosphatases, epigenetic targets, nuclear hormone receptors, GPCR, dehydrogenases, deacetylases, and demethylases.

Our experts understand your challenges and ensure meeting milestones on time and accelerating your discovery. Talk to us and learn more about our proven track record in each domain.

Reference:

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