Looking Under the Lamppost: The Search for New Cancer Targets in the Human Kinome

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Abstract—The number of cancer drugs is increasing as new chemical entities are developed to target molecules, often protein kinases, driving cancer progression. In 2009, Fedorov et al. identified that of the protein kinases in the human kinome, most of the focus has been on a small subset. They highlighted that many poorly investigated protein kinases were cancer drivers, but there was no relationship between publications and involvement in cancer development or progression. Since 2009, there has been a doubling in the number of publications, patents, and drugs targeting the kinome. To determine whether this was an expansion in knowledge of well-studied targets—searching in the light under the lamppost—or an explosion of investigations into previously poorly investigated targets, we searched the literature for publications on each kinase, updating Fedorov et al.’s assessment of the druggable kinome. The proportion of papers focusing on the 50 most-studied kinases had not changed, and the makeup of those 50 had barely changed. The majority of new drugs (80%) were against the same group of 50 kinases identified as targets 10 years ago, and the proportion of studies investigating previously poorly investigated kinases (<1%) was unchanged. With three exceptions [p38 mitogen activated protein kinase (p38a), AMP-activated protein kinase catalytic subunit 1,2, and B-Raf proto-oncogene (BRAF) serine/threonine kinase], >95% of publications addressing kinases still focused on a relatively small proportion (<50%) of the human kinome independently of their involvement as cancer drivers. There is, therefore, still extensive scope for discovery of therapeutics targeting different protein kinases in cancer and still a bias toward well-characterized targets over the innovative searchlight into the unknown.

Significance Statement—This study presents evidence that drug discovery efforts in cancer are still to some extent focused on a narrow group of well-studied kinases 10 years after the identification of multiple novel cancer targets in the human kinome. This suggests that there is still room for researchers in academia, industry, and the not-for-profit sector to develop new and diverse therapies targeting kinases for cancer.
I. Introduction

Multiple cellular functions are regulated by protein kinases (PK). These proteins orchestrate the amplification and propagation of cellular stimuli through signal transduction cascades, resulting in biologic responses. The deregulation of the activity of the almost 500 protein kinases encoded in the human genome can lead to various diseases, such as neurologic and inflammatory diseases, vascular disorders, and, in particular, cancer (Catapano and Manji, 2008; Chico et al., 2009; Zhang et al., 2009). Therefore, there has been an intense interest in identifying PKs that may be druggable.

PKs have been found to be potential targets to treat central nervous system disease (Chico et al., 2009). However, one of the key challenges in developing kinase inhibitors (KI) for central nervous system disorders is the blood-brain barrier penetration and selectivity (Gunosewoyo et al., 2017). Bipolar diseases have also been proposed to be targetable by druggable protein kinases, in particular glycogen synthase kinase-3 and protein kinase C (Catapano and Manji, 2008).

Nonetheless, most potential PK targets that have been investigated are targeted at cancer due to the high unmet medical need. In the past decade, much effort has been put into finding alternatives that can replace the cytotoxicity associated with conventional therapies, such as chemotherapy (Pucci et al., 2019). The primary chemotherapeutic agents are antimetabolites (e.g., methotrexate), DNAinteractive agents (e.g., cisplatin, doxorubicin), antitubulin agents (taxanes), and hormone targeting agents; however, they are not specific for cancer cells (Nussbaumer et al., 2011). Targeted therapies, in contrast, aim to block specific cancer-inducing pathways, or pathways specifically activated in cancer cells by different mechanisms, such as inducing apoptosis, interfering with cancer cell proliferation by blocking enzymes or growth factor receptors upregulated or activated in cancer cells or by modifying gene expression and other cellular functions. This can result in a less harmful and more effective approach compared with the toxic effects from chemotherapy on nontargeted tissues that can impair a patient’s quality of life (Joo et al., 2013; Choudhari et al., 2020).

Hence, there has been a noticeable paradigm shift toward identifying protein targets driving cancer. Imatinib, a Bcr-Abl tyrosine kinase inhibitor (TKI), was one of the first targeted therapies used to treat chronic myeloid leukemia (CML) (Sparreboom and Verweij, 2009). This type of cancer results from an overexpression of Bcr-ABL tyrosine kinase (TK) in cancer cells. This selective inhibitor could suppress cancerous cellular growth while reducing the harm inflicted upon healthy cells, ultimately providing a better approach to treat CML. This work eventually led to the identification of new drugs to treat solid tumors.

Since imatinib was approved by the U.S. Food and Drug Administration (FDA) on May 1, 2001, 141 new drugs have been approved for various cancers by July 2020, and the rate at which these drugs are coming through is accelerating (Fig. 1A; Supplemental Table 1). These drugs have many different mechanisms of action, including chemotherapies that target cell division in a nonspecific manner (12 drugs), immunotherapies (19 drugs), hormone inhibitors (eight drugs), and others, including radiotherapies (three), antibody drug conjugates (four), metabolic inhibitors (five), antibodies targeted to extracellular proteins (seven), DNA targeting agents (eight) such as Poly (ADP-ribose) polymerase (PARP) inhibitors, and epigenetic modulators and vaccines (one). However, the most common drugs are kinase inhibitors (43% of all inhibitors since imatinib), and these have become more common (Fig. 1B) in each of the last three years. Kinase inhibitors include agents that block the activity of protein kinases and some other proteins that act as kinases, such as the lipid kinases (e.g., PI3K). The percentage of drugs approved that are KIs has been steady at just under half of all new anticancer drugs for the last 15 years (Fig. 1C). Interestingly, these drugs are accounted for by just 19 kinases in the human genome and, of the 61 drugs approved for treatment of cancer, 75% are targeted against just 10 kinases with epidermal growth factor receptor (EGFR), vascular endothelial growth factor, BCR-Abl, human epidermal growth factor receptor 2, and anaplastic lymphoma kinase (ALK), accounting for half of all KIs approved for cancers (Fig. 1D; Supplemental Table 1).

A. A Case Study: Protein Kinases in Cancer Research

Protein phosphorylation catalyzed by both protein phosphatases and kinases plays a significant role in cancer. When such proteins are phosphorylated, the activity of the substrate is modified, leading to changes in specific cellular processes, such as cell cycle progression, gene transcription, cytoskeletal rearrangement and cell movement, cell metabolism, cell differentiation, and apoptosis (Manning et al., 2002). In cancer, many of these processes are altered, allowing cancer cells to proliferate excessively and escape mechanisms that normally control their survival and migration (Sever and Brugge, 2015).

The three-dimensional structures (Knighton et al., 1991) and kinetic and catalytic activity (Adams, 2001) of eukaryotic protein kinases, of which more than 500
are found in humans (Manning et al., 2002), have been intensively investigated for many years. More recent estimates of the size of the human kinome are larger (Wilson et al., 2018; Sugiyama et al., 2019); however, the most recent study shows that the human kinome compromises an extended set of 710 kinase domains and a more narrowly curated set of 557 protein kinase-like domains, including the eukaryotic PKs (Moret et al., preprint, DOI: https://doi.org/10.1101/2020.04.02.022277). From those hundreds of proteins, many have been critically linked to cancer, but only a few have approved anticancer drugs. In cancer, deregulated PKs are frequently found to be oncogenic, and cancer cells can become dependent on these signals that drive cell growth and promote survival. Different types of deregulations, such as misregulated expression and/or amplification, chromosomal translocation, aberrant phosphorylation, mutation, and epigenetic regulation, can result in dramatic changes in PK activity (Zawistowski et al., 2014; Sugiyama et al., 2019).

These changes in a cancer cell genome can also be considered driver or passenger, according to its consequences for cancer development. When a mutation confers growth advantages to cancer, it is considered a driver; whereas mutations that are present but do not confer growth advantages are considered passengers (Stratton et al., 2009). Many driver mutations are not major players in well-known signaling pathways but play critical roles in proliferation signaling pathways. In 2009, a publication from Federov et al., “The (un)targeted kinome” investigated whether published research is largely biased toward PKs with well-established roles in cellular signaling (Fedorov et al., 2010). This fact was not only true for PKs but also other gene families such as the “novel” nuclear receptors. This family was identified in the 1990s, and there was an increased interest to develop therapeutics due to their link to diseases. Over the next 15 years, research activity refocused on only a subset of eight of these receptors, although not having any genetic difference from the other 29 with known links to disease (Edwards et al., 2011).

**B. The Druggable Kinome.** Currently, PKs are a main target for the development of drugs, especially in cancer research, due to their ability to drive cancer by specific molecular pathways and the relative ease of druggability. A recent collective analysis of the target spectrum of various KIs defined the proportion of clinically viable kinases in the kinomic landscape that is druggable, ultimately referred to as the “druggable kinome” (Ravikumar et al., 2019). Within this data, it has been shown that the majority are Adenosine triphosphate (ATP)-competitive inhibitors (type I and type II KIs), which are typically more promiscuous compared with allosteric binders (type III and type IV KIs). The therapeutic and adverse effects associated with these

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**Fig. 1.** Cancer drug approvals since Imatinib was approved. (A) Cumulative number of new cancer drug approvals by FDA. (B) Drug approvals broken down by class. (C) Proportion (percent of total approvals) broken down by class. (D) Number of drug approvals of kinase inhibitors broken down by primary target.
KIs are related to such promiscuity, supporting a stringent efficacy/safety ratio in anticancer drug development strategies (Ravikumar and Aittokallio, 2018). To improve the success rate in clinical trials, it is critical to understand the chemogenomic space underlying the druggable kinome (Fedorov et al., 2010; Ravikumar et al., 2019) and, in particular, to determine whether research efforts over the last 10 years have been focused on “me-too” protein kinase inhibitors or whether there has been an increase in the number of studies investigating the role of novel PK targets to develop novel therapeutic strategies targeting PKs for which relatively little research has been done. In some cases, the “me-too” drug syndrome is related to the successive efforts to overcome resistance against earlier drug generations. For instance, there are currently five approved drugs targeting ALK (Kong et al., 2019) as well as for the approved EGFR TKIs (Solassol et al., 2019). Knapp et al. proposed a large-scale public-private partnership as a new approach that offers economies of scale, minimized redundancy, and sharing of risk and cost to overcome the high cost associated with probe generation, ultimately stimulating new drug discovery to address unmet medical needs in cancer, metabolism, inflammation, and other diseases (Knapp et al., 2013).

C. Hypothesis/Aim. We tested the hypothesis that recent research has been focused on looking at well-investigated cancer targets (“looking under the lamppost”) rather than branching out into new areas (“beyond the light under the lamppost”). To do this, we undertook a re-review of the literature, comparing work from 2009 to 2019 with that summarized by Federov et al. in 2009.

II. Material and Methods

The number of publications related to kinases was searched in the National Center for Biotechnology Information database Pubmed. This search was performed using the R (version 3.6.1) package `rentrez` (Winter, 2017). Given the wide range of acronyms kinases display in literature, the data from Manning et al. was used to match the kinases with every term (Manning et al., 2002). These acronyms have been updated for the newest discovered kinases and manually curated to avoid ambiguous terms. The search required the term “kinase” to appear anywhere in the published paper and the kinase acronym or full name to be present in the title or abstract to assign the publication to the kinase. Family names were not considered in the search, since it is difficult to discern a specific protein; whereas specific subunit mentions were assigned to the belonging protein. Finally, only unique publication identifiers were kept for each kinase. The code used and sample files can be found in the GitHub repository https://github.com/CrisRu95/Kinome.

The Protein Kinase Inhibitor Database (Carles et al., 2018) was used to search for kinase inhibitors, either approved or in clinical trials. Kinome tree images were generated using CORAL (Metz et al., 2018). The Catalogue of Somatic Mutations in Cancer (COSMIC) was used to link kinases with cancer.

III. Results

A. Validation of Methodology. The number of publications found by the search criteria presented in this paper is comparable to the number of publications found by the authors of “The (un)targeted kinome” (Fig. 2).

Using the data from Federov et al., we plotted the number of publications found using their methodology against the number of papers published up until 2009 using our search criteria and found a highly positive correlation (r = 0.83) (Fig. 2). This indicates that the search criteria for the two sets of data identifies a similar trend as well as set of publications.

B. Findings. We then compared the number of publications using our search criteria from 2009 to 2019, with those up to 2009. Figure 3A shows that there is a very high correlation (0.92) with a slope equal to 0.848±0.01; i.e., kinases that had a high number of publications up to 2009 were intensively published in the period since 2009. In fact, in 10 years the number of publications on these kinases was on average 85% of the total number of papers published in total up to that date, irrespective of how well-studied they were. For instance, protein kinase A catalytic subunit α (PKA-Cα) had 9168 publications up to 2009 but 6810 from 2009 to 2019. There were a few exceptions to this rule, which included the AMP-activated protein kinase catalytic α-subunit 1,2, BRAF, and
Fig. 3. Comparison between kinase publications. (A) Number of publications for each of the kinases found up to 2009 and number of publications found from 2009 to 2019 both with logarithmic transformation. The regression line is depicted in red. (B) Number of publications of each kinase up to 2019. The top 10 are depicted in a color scheme. (C) Comparison between the number of publications found up to 2009 (in gray) and up to 2019 (in black).
Fig. 4. Kinome map. (A) The top 10 most published kinases are depicted with large circles, the next 20 most published kinases with medium-sized circles, and the next 70 with small circles. (B) Drugged kinome map. The top 10 most cited kinases are depicted with large circles, the next 20 with medium-sized circles, and the next 70 with small circles. The kinases that are not targets of any inhibitory drug are shown in red; the kinases that have inhibitory drugs in clinical trials (phases 1, 2, and 3) are shown in blue, and kinases with FDA-approved inhibitors are depicted in green. Kinome tree image was generated using CORAL (Metz et al., 2018).
ALK kinases. ALK had nearly five times more studies published since 2009 than before; possibly this fact is related to the development of five new ALK inhibitors. These results indicate that the evolution of kinase research in the past 10 years (from 2009 to 2019) has generally followed a similar dynamic to the one described in “The (un)targeted kinome,” but that when a breakthrough does occur, it is reflected in the literature. A minority of kinases are extensively studied (Fig. 3B), whereas the rest remain mostly not investigated or unpublished. Figure 3C shows that eight of the 10 most cited kinases have remained the same for the last 10 years.

To further investigate where in the kinase family this research has focused, we mapped the most commonly published kinases onto the evolutionary tree of the kinase family of proteins (Fig. 4A). This shows that kinase research tends to focus mainly on the TK family and, to a lesser extent, on the Cyclin-dependent kinases (CDKs), Mitogen-activated protein kinases (MAPks), Glycogen synthase kinases (GSKs), and Cdc2-like kinases (CLKs) (CMCG group) [and specifically the cyclin-dependent kinase (CDK)] and A, G, and C serine/threonine kinases (AGC kinases). This clinical development of inhibitors of the kinase family follows the same trend; out of 25 kinases with approved KI in the last 10 years, 15 of them are from the TK family (Fig. 4B).

Finally, we looked to determine whether kinases classified as cancer drivers due to mutations, knockdown, or overexpression have been the focus for new investigations (Fig. 5, A and B). The results indicate...
cancer driver genes not well investigated before 2009 were not especially researched in the next 10 years. When we extended this to use the COSMIC database, we found similar results. The most studied cancer drivers up until 2009 are still the most studied cancer drivers, with extracellular signal-regulated kinase 2, EGFR, SRC proto-oncogene (SRC) non-receptor tyrosine kinase, protein kinase A catalytic subunit \( \alpha \), and Human epidermal growth factor receptor 2 (HER2) (also known as ERBB2) (HER2/ErbB2) in the top five cancer driver genes. The most studied cancer drivers up until 2009 are still the most studied cancer genes. The receptor-interacting protein kinase 3 inhibitors, and several trials are ongoing although mostly for noncancer indications (Benn and Dawson, 2020). Additionally, the Hippo pathway was discovered more than a decade ago and its signaling cascade was described (Yu and Guan, 2013); however, recent studies have uncovered novel kinases involved in the pathway, such as members of the Ste20-like Mitogen-activated protein kinase 4 (MAPK4) family and the AGC threonine Nuclear Dbf2-related kinase 1 and 2 (NDR1/2) kinases (or Serine/threonine kinase 38 (ST K38)/Serine/threonine kinase 38 like (STK38L)) (Hergovich, 2016).

We like to think of research as being systematic and organized, but funding could be an important barrier to individual-level research when embarking on studying those neglected proteins. Funded research is often granted to study proteins with significant pre-existing background that support defined hypotheses. The lack of funding supporting more risky and exploratory research could explain our findings.

Given the call to action by Knapp et al. and Edwards et al. 10 years ago, the lack of evidence that the field has made the major effort over the past 10 years to initiate investigations of understudied PKs might be considered surprising (Edwards et al., 2011; Knapp et al., 2013). However, switching to a new PK and publishing meaningful science on it can be a slow process, particularly for pharma/biotech companies, where bringing a new drug against a new target PK into trials and then to market often takes 10 years. In consequence, one might not expect to see a rapid influx of papers describing drugs targeting understudied PKs. Inhibitors against several lesser-studied PKs have been approved in the past five years, including tropomyosin receptor kinase A (Saleh et al., 2019), Ret Proto-Oncogene (RET) receptor tyrosine kinase (Biotechnology, 2020), and spleen tyrosine kinase (Mulard, 2018), and there are over 200 protein kinase inhibitor clinical trials underway, including several with drugs targeting relatively understudied protein kinases, such as WEE1 G2 Checkpoint kinase (WEE1) (Liu et al., 2021), ATR Serine/Threonine kinase, Protein kinase, DNA-activated, catalytic subunit (DNA-PK) (van Bussel et al., 2021), interleukin 1 receptor associated kinase 4 (Wiese et al., 2020), and Mitogen-activated protein kinases-interacting kinases 1 and 2 (MNK1/2) (Jin et al., 2021).

Even though the future of protein kinase-targeted therapeutics in cancer appears promising, researchers have the tendency to study “what is easier to study,” creating a bias toward well-studied PKs and possibly overlooking promising targets. Also, new opportunities for PK target discovery could emerge from discovering new relevant pathways instead of investigating a new undiscovered PK. For instance, the mammalian unc-51 like autophagy activating kinase 1 is now being studied due to its essential role in initiating macroautophagy/autophagy (Li et al., 2020), and one class of unc-51 like autophagy activating kinase 1/2 kinase inhibitors has recently been licensed for clinical development. Although autophagy was found more than 50 years ago, only within the last decade has a variety of research elucidated the molecular basis behind autophagy and its role in driving cancer. The receptor-interacting protein kinase 3 and the mixed lineage kinase domain like pseudokinase are other examples that have coemerged with the extensive study of necroptosis (He et al., 2016). There are currently intensive pharma efforts to develop receptor-interacting protein kinase 3 inhibitors, and IV. Discussion

Here, we have examined the most studied kinase within the scientific community and how this has changed over the period of 10 years. We found that the majority of publications still focus on a relatively small proportion of the human protein kinases regardless of their relevance in cancer. We also observed that the vast majority of new FDA-approved drugs target the same top 50 most-studied PKs, and that these protein kinases belong to the same PK families. Interestingly, many protein kinases reported to be cancer drivers 10 years ago have not yet been explored; for instance, driver mutations were first identified in 2005 for Serine/threonine-protein kinase H2 (Davies et al., 2005) and two years later for Serine/threonine kinase 32A (YANK1) (Greenman et al., 2007), but these are still mostly unstudied. Other kinases, such as Cyclin dependent kinase 15 (PFTAIRE2) or Doublecortin like kinase 3 (DCAMKL3), also already classified as cancer drivers in Fedorov et al.’s paper (2010), show a similar trend.

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appropriate indication for a specific PK target is very often hampered by the fact that there are not robust preclinical models for all the various cancers and cancer stages with some exceptions. Therefore, these clinical attributes could also explain the lamppost effect.

The importance for academic researchers of establishing promising programs, likely to be funded and with a high likelihood of leading to publishable outputs, is a factor that could create a confirmation bias by further investigating existing known targets, rather than taking risks on targets that are less widely known. The same applies in industry—known targets may be more likely to be supported, and so researchers proposing new programs in industry are more likely to progress if they push incremental (but not “me-too”) programs. This means incremental research is rewarded over genuinely innovative, high-risk research. The decision to fund research is usually taken by senior management within the pharmaceutical industry or by funding panels and agencies, based on proposals brought to them either externally or internally. Thus, both the decision to submit proposals and the decision-making on whether to fund these programs would be affected by such confirmation bias. Lack of human target validation of the activity of these PKs in disease, poorer understanding of their roles in disease, and the lack of existing drug programs in these areas may paradoxically deter both researchers and funders/decision makers from going after these PKs as the risks are perceived to be higher by both funders/funding decision makers and researchers.

Moreover, when a research project has been funded and a new drug class has emerged from that study, it can take a substantial amount of time for that class to be tested and approved. For instance, it has taken 20 years to understand how to treat EGFR and receptor tyrosine kinase driven cancers and their resistance to these protein kinase drug therapies. In addition, it is difficult to extrapolate potential benefits of an EGFR inhibitor used to treat epithelial lung cancer with an Proto-oncogene (ABL) nonreceptor tyrosine kinase inhibitor in the chronic phase of CML. Additionally, CDKs inhibitors were developed to treat cancer over the past 20 years (Whittaker et al., 2017; Roskoski, 2019), but it is not been until recently that the third generation CDK inhibitors (palbociclib, ribociclib, and abemaciclib) have received regulatory approval from the FDA for the treatment patients with breast cancer (Yuan et al., 2021). Other inhibitors that may change this are in the pipeline, i.e., inhibitors targeting Checkpoint kinase 1/2 (CHEK1/2), edc-like kinase 2 (CLK2), and CDK2 (Cyclin dependent kinase 2), and the rise of new drug-like macrocycles could also enable poorly investigated PKs, as its potential as oncology drugs is already evident, with some recent examples such as the Mechanistic target of rapamycin (mTOR) kinase inhibitor temsirolimus (Mallinson and Collins, 2012). Additionally, small-molecule drugs that inhibit Janus kinases (jakinibs), have gained traction as safe and efficacious options for the treatment outside oncology, like immune and inflammatory diseases (Schwartz et al., 2017), and could perhaps be used for targeting this small proportion of the human PKs.

Despite the aforementioned cases, a radical shift in exploration is not yet apparent—in general we are still looking under the lamppost. Information on clinical trials of small-molecule kinase inhibitors showed that only 30% of the human kinome is being targeted (Attwood et al., 2021). It is indeed important to increase our knowledge of well-studied and characterized targets, but there is still extensive scope for discovery of new protein kinase inhibitors against poorly investigated protein kinases. Perhaps, a focus on these poorly investigated protein kinases would enhance our knowledge of the cancer kinome and provide hope for patients with limited treatment options, resulting in a better outcome compared with the available treatments.

As of January 2022, there are now 87 small molecules and 11 monoclonal antibodies that block receptor TK signaling approved worldwide, with 66 kinase inhibitors approved for cancer therapy worldwide (although not all of them FDA-approved). Additionally, asciminib, an allosteric BCR-ABL inhibitor used for treating TKI-resistant BCR-ABL patients, has recently been approved by the FDA, bringing the anticancer kinase inhibitor total to 67 (Attwood et al., 2021).

Genome wide loss-of-function CRISPR/Cas9 screens are beginning to uncover neglected PKs as candidate cancer targets (Wiese et al., 2020). Genome/kinome-wide cancer sequencing efforts have also implicated mutations in understudied protein kinase genes in cancer, although further analysis has shown these mutations to be loss of function mutations, implying that these PKs may act as tumor suppressors and therefore would not merit future study as potential cancer drug targets. However, this approach could be really promising for searching new targets in the human kinome.

This lamppost effect has given rise to a project within National Institutes of Health’s Illuminating the Druggable Genome (Finan et al., 2017) Program to investigate the understudied “dark kinome” and determine its role in human biology and disease (Moret et al., preprint, DOI: https://doi.org/10.1101/2020.04.02.022277). The Dark Kinase Knowledgebase (https://darkkinome.org), initiated in 2017, is specifically focused on providing data and reagents for three protein families: the ion channels, G-protein-coupled receptors, and PKs, with a large component dedicated to underserved PKs. Drugs against the “dark kinome” seem also likely to emerge in the next few years by approaches to identify
candidate small molecules/drugs against understudied PKs in silico (Ravikumar et al., 2019). Such initiatives are likely to radically increase the amount of information published on understudied PKs and determine these potentially high-impact druggable targets, which may move research from looking under the lamppost.

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Authorship Contributions

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