Review

Leveraging Data from Spontaneous Animal Disease Models to Streamline Pharmaceutical Research: A Tale of Two Species

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Leveraging Data from Spontaneous Animal Disease Models to Streamline Pharmaceutical Research: A Tale of Two Species

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Abstract: According to data from the U.S FDA, the likelihood of a new drug progressing from Phase I clinical trials to market approval is only 8% (DiMasi et al., 2016). Furthermore, a significant attrition rate of 35% occurs during Phase II studies due to the failure to demonstrate clinical efficacy (Arrowsmith, 2011). These statistics underscore the urgent need to reassess the current research and development (R&D) paradigm. To address this challenge, a promising approach called reverse translational pharmacology (RTP) has emerged, aiming to enhance the predictive value of preclinical models used in biomedical research by leveraging animal models that spontaneously develop analogous diseases to humans (Schneider et al., 2018). The rationale behind RTP is that knowledge gained from clinical trials in canines can subsequently inform and guide human clinical trials, leading to improved outcomes for both species. Additionally, this approach capitalizes on the opportunity to stimulate veterinary drug development by leveraging pharmacokinetic (PK), efficacy, and safety data obtained from human clinical studies (Schneider et al., 2018). The application of reverse translational pharmacology holds immense potential for expediting drug development and advancing medical knowledge. By employing animal models that naturally develop diseases akin to those found in humans, researchers can enhance the predictive capacity of preclinical models, thereby mitigating the high attrition rates encountered in later stages of clinical trials. Moreover, the exchange of knowledge and data between human and veterinary medicine engenders a synergistic relationship, fostering progress in both domains (Schneider et al., 2018). As this innovative approach gains momentum, fostering collaborations between basic and clinician scientists, pharmaceutical companies, and veterinary professionals becomes increasingly imperative. By sharing resources, expertise, and findings, we can pave the way for groundbreaking discoveries and the development of safe and efficacious treatments for diverse diseases. Embracing reverse translational pharmacology offers an avenue to redefine the R&D paradigm, bringing us closer to a future where a higher proportion of drugs successfully traverse the arduous path from the laboratory to market approval, ultimately benefiting patients across species. In this brief commentary, we highlight four examples of diseases where reverse translational modeling has been used to support pharmaceutical research, including some applications developed in our research laboratory (SMART Pharmacology) at the Iowa State University College of Veterinary Medicine. In doing so, this report also seeks to provide a brief overview of the heuristic value of computational approaches in comparative research. To further illustrate the value of these in silico approaches, we deliberately chose to employ some features of ChatGPT to produce the present summary (OpenAI. (2023). GPT-3.5 [ChatGPT]. Retrieved from https://openai.com).

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1. Introduction

According to data from the U.S FDA, the likelihood of a new drug progressing from Phase I clinical trials to market approval is only 8% (DiMasi et al., 2016). Furthermore, a significant attrition rate of 35% occurs during Phase II studies due to the failure to demonstrate clinical efficacy (Arrowsmith, 2011). These statistics underscore the urgent need to reassess the current research and development (R&D) paradigm. To address this challenge, a promising approach called reverse *translational pharmacology* (RTP) has emerged, aiming to enhance the predictive value of preclinical models used in biomedical research by leveraging animal models that spontaneously develop

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analogous diseases to humans (Schneider et al., 2018). The rationale behind RTP is that knowledge gained from clinical trials in canines can subsequently inform and guide human clinical trials, leading to improved outcomes for both species. Additionally, this approach capitalizes on the opportunity to stimulate veterinary drug development by leveraging pharmacokinetic (PK), efficacy, and safety data obtained from human clinical studies (Schneider et al., 2018). A few exemplary instances where reverse translational modeling has effectively supported pharmaceutical research efforts include:

1. **Canine Osteosarcoma**: Osteosarcoma, a prevalent malignant bone tumor in humans, also afflicts canines (Fan and Khanna, 2015; Simpson et al., 2017). By investigating the similarities between human and canine osteosarcoma, scientists have successfully exploited the canine model to evaluate potential therapeutic candidates. These investigations have not only contributed to elucidating disease progression and identifying novel targets but have also facilitated the assessment of drug efficacy (Vancil et al., 2012).

2. **Feline Immunodeficiency Virus** (FIV): FIV is a viral infection in cats that closely resembles HIV infection in humans. By utilizing this naturally occurring feline model, researchers have leveraged data to investigate the pathogenesis of the virus, evaluate antiviral therapies, and gain insights into viral evasion mechanisms and immune responses (Elder et al., 2010). The findings from these investigations have significantly contributed to our understanding of HIV/AIDS, resulting in the development of potential treatments and preventive strategies for both feline and human patients (Yamamoto et al., 2010; Sahay and Yamamoto, 2018).

3. **Spontaneous Canine Epilepsy**: Canine epilepsy exhibits similarities to human epilepsy in terms of clinical manifestations, seizure types, and response to antiepileptic drugs. Through the study of dogs naturally affected by epilepsy, scientists have achieved a deeper understanding of the underlying mechanisms and identified potential therapeutic targets (Patterson et al., 2005). These discoveries have not only improved the management of epilepsy in canines but have also accelerated the development of novel treatments for human epilepsy, benefiting both species (Löscher, 2013).

The application of reverse translational pharmacology holds immense potential for expediting drug development and advancing medical knowledge. By employing animal models that naturally develop diseases akin to those found in humans, researchers can enhance the predictive capacity of preclinical models, thereby mitigating the high attrition rates encountered in later stages of clinical trials. Moreover, the exchange of knowledge and data between human and veterinary medicine engenders a synergistic relationship, fostering progress in both domains (Schneider et al., 2018).

As this innovative approach gains momentum, fostering collaborations between basic and clinician scientists, pharmaceutical companies, and veterinary professionals becomes increasingly imperative. By sharing resources, expertise, and findings, we can pave the way for groundbreaking discoveries and the development of safe and efficacious treatments for diverse diseases. Embracing reverse translational pharmacology offers an avenue to redefine the R&D paradigm, bringing us closer to a future where a higher proportion of drugs successfully traverse the arduous path from the laboratory to market approval, ultimately benefiting patients across species.

In this brief commentary, we highlight four examples of diseases where reverse translational modeling has been used to support pharmaceutical research, including some applications developed in our research laboratory (*SMART Pharmacology*) at the *Iowa State University College of Veterinary Medicine*. In doing so, this report also seeks to provide a brief overview of the heuristic value of computational approaches in comparative research. To further illustrate the value of these in silico approaches, we deliberately chose to employ some features of *ChatGPT* to produce the present summary (OpenAI. (2023). GPT-3.5 [ChatGPT]. Retrieved from https://openai.com).

2. Cancer Research

About six million dogs are diagnosed with cancer each year (Jacob, 2016), and more than half of dogs above the age of ten will develop cancers, such as lymphoma (Mochel et al., 2019), osteosarcoma (Fan and Khanna, 2015), melanoma (Atherton et al., 2016) or chemodectoma (Coto et al., 2021), among others (Jacob, 2016). As emphasized multiple times by the National Cancer Institute, mice often fail to adequately represent crucial features of human cancer, including genomic instability and tumor

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heterogeneity (Gordon et al., 2009). To address this challenge, researchers have turned to canine clinical trials, capitalizing on the high genetic homology between dogs and humans to advance cancer therapies.

One remarkable example of successful reverse translational pharmacology is the study of interleukin-12 (IL-12) in canine clinical trials for malignant melanoma. The substantial genetic similarity between canine and human IL-12 prompted researchers to investigate its pharmacokinetic (PK), pharmacodynamic (PD), efficacy, and toxicity profiles in dogs with melanoma (Paolini et al., 2015). The results of the study demonstrated that high levels of IL-12 could be safely administered subcutaneously to dogs with malignant melanoma, leading to both systemic immunological and clinical activity (Paolini et al., 2015). These findings played a pivotal role in guiding the decision to proceed with a Phase I clinical trial in humans.

Moreover, preliminary studies focusing on IL-12 gene electrotransfer in dogs with melanoma have yielded promising results for the treatment of spontaneous canine tumors (Lampreht et al., 2015). By harnessing the unique opportunity provided by naturally occurring melanoma in dogs, researchers have gained valuable insights into the therapeutic potential of IL-12 gene therapy, which may ultimately be applicable to human patients as well.

Muscle-Invasive Bladder Cancer (MIBC) is associated with an extremely poor survival rate of about 50% at 5 years follow-up, which, importantly, has not improved over the last 10 years (Patel et al., 2020). Two important factors that contribute to poor treatment outcomes are (1) the phenotypic and molecular heterogeneity of MIBC, which limits the translational value of some rodent models to evaluate therapeutic drug efficacy, and (2) the time it takes to test novel drugs and combinations of drugs in clinical trials for MIBC. As opposed to mice, canine MIBC constitutes an ideal preclinical study population to evaluate novel therapeutic options for patients with bladder cancer. In fact, canine MIBC presents with very similar molecular features, tumor heterogeneity and subtypes, as well as clinical and metastatic behavior as humans (Knapp et al., 2014). Although clinical trials in dogs with MIBC can be performed in significantly shorter timeframes than in people, so far, only very few large-scale trials using the canine model have been performed. Validation of predictive ex vivo assays to evaluate the potential efficacy of novel treatment modalities before formal testing in canine clinical trials will therefore enhance translational efforts for the development of novel therapeutics. A promising technology for the preclinical screening of candidate drug efficacy lies in the culture of patient-derived tumor organoids (PDOs) (Elbadawy et al., 2019; Mastri et al., 2021; Xie and Song, 2023). Compared with 2D cell lines, 3D PDOs better reflect the underlying biology of the tumor and are therefore considered more robust models to accurately predict clinical response to treatment compared with molecular testing alone. We therefore propose that future therapeutic leads for MIBC be screened ex vivo using canine organoids to select the most promising drug candidates. Subsequently, these novel therapeutics could be tested in vivo in dogs with bladder cancer prior to clinical testing in human patients with MIBC.

The importance of these canine clinical trials in advancing cancer therapies cannot be overstated. Through reverse translational pharmacology, researchers have been able to overcome some of the limitations of traditional preclinical models, ultimately improving the chances of success in human clinical trials. The insights gained from canine studies have the potential to transform the drug development pathway, providing a more accurate representation of disease processes and treatment responses. Altogether, the utilization of canine clinical trials has emerged as a powerful tool in advancing cancer therapies. By leveraging the genetic similarities between dogs and humans, researchers have successfully evaluated the safety, efficacy, and pharmacological properties of novel treatments, including immunotherapies (Park et al., 2016; Mason et al., 2021; Ammons et al., 2023). The findings from these reverse translational studies have not only guided the design of human clinical trials but also provided valuable insights into the treatment of spontaneous canine tumors. As we continue to explore the potential of reverse translational pharmacology, collaborations between basic and clinical scientists, pharmaceutical companies, and veterinary professionals will be pivotal in translating these discoveries into tangible benefits for both human and canine patients. A future step in that direction would be to generalize computational approaches for characterizing the

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pharmacokinetics and pharmacodynamics of anticancer drugs used alone or in combination, as previously described in the human literature (van Hasselt and Iyengar, 2018; Zhu, 2018; Aghamiri et al., 2022; Lam et al., 2022), including data originating from our group (Schneider et al., 2018; Vaghi et al., 2020).

3. Inflammatory Bowel Disease

Inflammatory Bowel Disease (IBD) is a chronic and prevalent disorder characterized by inflammation in the gastrointestinal tract. It affects both humans and dogs, and interestingly, dogs with IBD share remarkable similarities with human patients in terms of clinical symptoms and molecular pathways involved in the disease (Jergens, 1999; Cerquetella et al., 2010; Honnefer et al., 2014; Atherly et al., 2019; Allenspach and Mochel 2021). This parallelism presents an excellent opportunity for the application of reverse translational modeling to enhance our understanding and treatment of IBD. The application of reverse translational modeling in IBD research has several advantages. Firstly, by using dogs as a disease model, researchers can gain insights into the pathophysiology of IBD in a more clinically relevant context. Dogs naturally develop spontaneous cases of IBD, allowing for the investigation of disease progression and response to treatment in a manner that closely mirrors human patients. This provides a valuable opportunity to evaluate the efficacy and safety of potential therapeutics and refine treatment protocols before translating them to human clinical trials.

A recent collaborative study between Iowa State University and the University of Navarra employed a network systems approach based on Boolean equations to model IBD (Balbas-Martinez et al., 2017, 2018). This mathematical modeling technique allows for the construction of a network of interactions between different molecular components involved in the disease. These models can capture the intricate interactions between multiple molecular components and provide predictions about the effects of perturbations or interventions. By integrating experimental data and computational simulations, researchers can optimize treatment strategies, identify key molecular targets, and minimize the potential risks associated with clinical trials. By simulating these interactions, researchers can gain insights into the underlying mechanisms and identify potential therapeutic targets. In this study, the focus was on the purinergic receptor P2X7, which has been implicated in the inflammatory response in IBD. By using the model, we aimed to simulate the effect of a non-competitive antagonist of the P2X7 receptor and determine the optimal dose for an upcoming clinical trial in dogs diagnosed with IBD. This approach holds promise for refining the dosing strategy and increasing the chances of success in clinical trials.

There is currently no cure for IBD and many therapeutic interventions developed over the past three decades have consistently failed to demonstrate evidence of efficacy in canine clinical trials (Makielski et al., 2019). There is, therefore, a *critical need* to develop robust drug screening tools to accelerate the availability of effective and safe therapeutic strategies for management of canine IBD. Our research group has focused on the development of canine intestinal organoids to enhance our understanding of disease pathogenesis and to screen novel therapeutic drug candidates (Ambrosini et al., 2020; Kopper et al., 2021; Gabriel et al., 2022a, 2022b).

Organoids (2017 *Nature* Method of the Year and 2018 *Science* Breakthrough of the Year) are sampled from individuals with different genotypes, environmental risk factors or drug sensitivity profiles, thereby reflecting the diversity of the disease background across many demographics. The biologic potential of 3D organoids is derived from the method's ability to harness hard-wired cellular programming within higher order cellular tissue organization to *more predictably evaluate drug activity* in vitro compared with conventional 2D systems (Fatehullah et al., 2016). Recent research from the WSAVA emphasized that *cellular* and *architectural* changes of the *epithelium* were the most *important determinants of disease pathogenesis* in IBD (Day et al., 2008; Allenspach et al., 2019). Therefore, developing methods focusing on the epithelial cell layer, such as organoids, will provide key information for understanding disease mechanisms in canine IBD. A promising development in this regard derives from our recent findings demonstrating that stem cell-derived intestinal organoids can be replicated ex vivo in dogs with IBD (Mochel et al., 2017; Chandra et al., 2019; Sahoo et al.,

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2022). This is a significant step toward the development of a completely new animal disease model for veterinary research, with the added benefit that data generated in dogs can be used to streamline similar clinical trials in human patients with IBD (Hong et al., 2017). This research is part of a broader 5-year research collaboration agreement (RCA) with the Office of New Animal Drug Evaluation (ONADE) of the FDA. This RCA is targeted at characterizing the intestinal permeability of a range of compounds in 3D canine organoids. To reach that goal, we first had to establish successful culture of organoids in a confluent monolayer using transwells. Our laboratory has just completed a first series of passive permeability assays in large intestinal organoids with metoprolol, propranolol, atenolol, and FITC-dextran, and benchmarked our results vs. conventional 2D systems, such as Caco-2 cells (Sahoo et al., 2023). Predictions of apparent permeability (Papp) parameters derived by the FDA were consistent with previously published literature. With successful completion of this first milestone, we are now evaluating the predictive performances of 3D organoids to model active drug transport.

The application of reverse translational modeling in the study of IBD holds significant promise for advancing our understanding and treatment of this complex disease. By leveraging the similarities between dogs and humans in terms of clinical presentation and molecular pathways, scientists can gain valuable insights into disease mechanisms and develop more effective therapeutic strategies. The integration of mathematical modeling techniques further enhances our ability to simulate and predict the effects of interventions, optimizing the design and outcomes of clinical trials. Through collaborative efforts and innovative approaches, reverse translational modeling in IBD research offers great potential for improving patient outcomes in both veterinary and human medicine.

4. Ocular Diseases

The ocular surface plays a critical role in maintaining the health and integrity of the eye. It is a complex and dynamic system consisting of the secreted tear film, lacrimal gland(s), eyelids, meibomian glands, cornea, conjunctiva, sclera, and nasolacrimal drainage apparatus. In a recent review by our group (Sebbag and Mochel, 2020), we have highlighted how the canine ocular surface closely resembles the human ocular surface in terms of anatomical structure, tear film composition, and immune responses. Dogs naturally develop a range of ocular surface disorders, such as dry eye syndrome, keratoconjunctivitis sicca, and corneal ulcers, which share similarities with their human counterparts. By studying these conditions in dogs, clinician scientists can gain insights into the underlying mechanisms, pathology, and potential therapeutic interventions. Specifically, several studies originating from our lab have investigated various aspects of ocular health and tear composition in different animal models, providing valuable insights into ophthalmic research. In a seminal study, Sebbag et al. (2018) evaluated the impact of flow rate, collection devices, and extraction methods on tear concentrations following oral administration of doxycycline in dogs and cats. They found that different collection methods influenced tear concentration measurements. In another study, Sebbag et al. (2019) investigated the kinetics of fluorescein in the tear film of beagle dogs after eye drop instillation. They examined the role of droplet size and its impact on tear film dynamics, suggesting that droplet size may not significantly affect tear clearance. Histamine-induced conjunctivitis and breakdown of the blood-tear barrier in dogs were later explored as a model for ocular pharmacology and therapeutics by Sebbag et al. (2019). The study provided insights into the mechanisms underlying ocular inflammation and suggested potential therapeutic strategies. Uhl et al. (2019) focused on cats and described the clinical features of cats with aqueous tear deficiency. The retrospective case series highlighted the diagnostic and management challenges associated with this condition in feline patients. Other studies investigated tear collection methods and their impact on tear composition. Bertram et al. (2021) examined the influence of Schirmer strip wetness on tear volume and total protein content in canine tears. The authors found that tear volume absorbed and recovered by the Schirmer strip, as well as total protein content, were influenced by the wetness of the strip. At last, Terhaar et al. (2021) focused on horses and evaluated serum albumin and total protein concentration in the tear film of horses with healthy or diseased eyes. Their findings indicated differences in tear protein composition between healthy and diseased eyes in horses.

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Collectively, these studies demonstrate the diverse research conducted in the field of comparative ophthalmology, utilizing different animal models to investigate tear composition, ocular diseases, drug delivery, and tear collection methods. These findings contribute to our understanding of ocular health and provide valuable insights for the development of ophthalmic therapies and diagnostic approaches.

5. Congestive Heart Failure

Congestive heart failure (CHF) is a complex condition that affects both humans and dogs, and its development often involves the overactivation of the renin-angiotensin-aldosterone (RAA) pathway (Watkins et al., 1976; Roig et al., 2000, Güder et al., 2007; Mochel and Danhof, 2015). Understanding the dynamics of RAA biomarkers and their response to treatment is crucial for optimizing therapeutic strategies. In a seminal study by our group, the potential effect of chronobiology and food intake on the pharmacodynamic of angiotensin-converting enzyme (ACE) inhibitors such as benazepril was further discussed (Mochel et al., 2013a, 2014). This study revealed that the timing of food intake plays a significant role in synchronizing the RAA pathway in dogs, suggesting that the administration of ACE inhibitors should be adjusted based on the time of food intake. This finding is of particular importance as it highlights the need for individualized dosing regimens that take into account the influence of food on drug absorption and the subsequent modulation of RAA biomarkers.

Contrary to previous assumptions that ACE activity alone could reliably predict RAA activity, Mochel et al. (2013b, 2013c, 2015) established that ACE activity alone is not sufficient to gauge the overall activity of the RAA pathway in dogs. This finding aligns with previous studies conducted in human patients with CHF, underscoring the complexity and multifaceted nature of RAA regulation (Van de Wal et al., 2006). The use of a semi-mechanistic PK/PD model in this other study represents a significant advancement in our understanding of the interplay between food intake, drug administration, and RAA activity in dogs. PK/PD models allow for the integration of pharmacokinetic data (drug concentration profiles) with pharmacodynamic measurements (biomarker responses) to provide insights into the relationship between drug exposure and its effects on the biological system. Little is known about the optimal dosing of the ACEI benazepril in dogs with CHF. Seminal studies (Toutain et al., 2000; King et al., 2003) had initially suggested that the pharmacological action of benazepril was relatively independent of doses > 0.25 mg/kg P.O, thereby providing a rationale for the current European label dose of 0.25 mg/kg P.O q24h in dogs with cardiovascular diseases. However, most of these earlier studies on benazepril pharmacodynamics relied on measures of ACE activity, which is a sub-optimal endpoint to characterize the effect of benazepril on the RAAS (Mochel and Fink., 2013). Quantitative systems pharmacology (QSP) modeling is an established framework for characterizing the effect of therapeutic drugs on complex biological systems, such as the renin-angiotensin cascade (van der Graaf and Benson, 2011). Importantly, by simulating virtual clinical trials from such a model, one can directly and quantitatively predict the effects of various hypothetical dosing schedules for therapeutic optimization purposes. By employing this modeling approach, scientists can now simulate different scenarios and optimize dosing strategies to achieve desired therapeutic outcomes. In the most recent publication from our group, this approach was used to develop a software implementation of the benazeprilat-RAAS QSP model, which is capable of rapidly simulating clinical trials for optimal dosing of ACEI at the bedside (Schneider et al., 2023). Using this simulation engine, we could predict and quantify the effect of varying dosing schedules of benazepril on the classical and alternative arm of the RAAS on top of diurnal variations. By developing an easy-to-use simulation interface for our model, we are now able to make a first prediction of the optimal dose/time of benazepril administration in dogs in support of future investigations in patients with CHF.

Altogether, these research studies sheds light on the intricate dynamics of the RAA pathway in dogs and its modulation by food intake. The findings emphasize the importance of adjusting dosing regimens of ACE inhibitors according to the timing of food intake in order to optimize therapeutic outcomes. Furthermore, the study challenges the notion that ACE activity alone can serve as a reliable

predictor of RAA activity in dogs, reinforcing the complexity of RAA regulation in CHF. These insights, gained through the application of semi-mechanistic PK/PD modeling, contribute to the development of tailored treatment strategies for CHF in both veterinary and human medicine. One such example of our search for new therapeutic drugs in the field involves our work on the pharmacokinetics and pharmacodynamics of the angiotensin receptor–neprilysin inhibitor (ARNi) LCZ696 (Mochel et al., 2019).

6. Conclusions

Reverse translational pharmacology represents a promising approach to enhance preclinical models and facilitate the development of effective therapeutics for both human and veterinary use. By utilizing animal models that spontaneously develop diseases analogous to those in humans, researchers can improve the predictability of preclinical studies, leading to better characterization of drug efficacy and safety.

To achieve success in reverse translational pharmacology, collaboration and cross-disciplinary communication are crucial. Quantitative scientists, human health specialists, and animal health experts need to work together to exchange knowledge, share insights, and collectively design studies that address the specific needs of both human and veterinary medicine. This collaborative approach allows for the identification of shared molecular targets, evaluation of therapeutic interventions, and the establishment of parallel drug development programs for human and veterinary species.

Additionally, regulatory incentives play a vital role in promoting the adoption of reverse translational pharmacology. Regulatory agencies can provide guidance and support for the development of parallel drug development programs, acknowledging the value of veterinary studies in advancing human medicine. By recognizing the potential benefits of reverse translational modeling, regulators can encourage researchers and pharmaceutical companies to invest in this approach, leading to improved drug development strategies and better outcomes for both human and veterinary patients.

In summary, reverse translational pharmacology holds great promise in refining the drug development process by leveraging the similarities between human and veterinary diseases. By fostering collaboration, promoting regulatory incentives, and emphasizing the importance of cross-disciplinary approaches, researchers can unlock the full potential of reverse translational pharmacology, ultimately improving the selection and efficacy of therapeutics for a wide range of diseases in both humans and veterinary species.

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