EDITORIAL

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Challenges to the translation of basic science findings to atrial fibrillation therapies

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“Although recent data suggest that ... atrial fibrillation therapy has improved in recent years, it remains suboptimal ... for both forms of rhythm control, which show limited efficacy and potentially severe side effects.”

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Atrial fibrillation (AF) strongly impacts present day cardiovascular care, affecting an estimated 33.5 million people worldwide. AF increases morbidity and mortality, predominantly as a risk factor for stroke and worsening heart failure [1,2]. AF is considered a progressive disease and is typically classified as paroxysmal, persistent or long-lasting persistent (chronic) based on the duration of episodes. The incidence of AF is expected to increase significantly in the upcoming years due to the ageing of the population, larger abundance of risk factors and improved detection, substantially increasing healthcare costs [1]. Current AF therapy involves antithrombotic therapy to reduce stroke risk and control of ventricular activation rate (rate control) [2]. In addition, cardioversion and subsequent sinus rhythm maintenance (rhythm control), predominantly through pharmacological approaches or ablation, are applied to symptomatic patients [2]. Although recent data suggest that overall AF therapy has

improved in recent years, it remains suboptimal, particularly for both forms of rhythm control, which show limited efficacy and potentially severe side effects [3,4].

There is a long-standing history of basic research in AF (reviewed in [1,5–6]). A better understanding of AF is expected to facilitate development of improved therapeutic approaches [6]. We have recently provided a critical analysis, highlighting the prominent role that basic insights have already played in current AF therapy, but also identifying a substantial translational gap [6]. Here, we will briefly summarize four important challenges in the translation of basic science findings to improved therapy and management and highlight recent discoveries that show promise for future improved mechanism-based AF therapy.

It remains challenging to identify ‘multiscale’ AF mechanisms

A detailed understanding of AF pathophysiology from molecule to patient is

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- translation

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likely required for effective therapy. At present, most research has focused on the two extremes of this scale: cellular and molecular mechanisms as basis for novel antiarrhythmic drugs and *in vivo* imaging/mapping of AF manifestation to guide ablation.

It is obvious that the development of improved antiarrhythmic therapy requires detailed understanding of the molecular AF mechanisms to identify drugable targets. Since arrhythmias are an intrinsically multicellular phenomenon, the function of a single molecular target strongly depends on its environment and regulation *in vivo*. The molecular determinants of atrial arrhythmogenesis remain incompletely understood, but recent work has identified novel components that might represent potential therapeutic targets, including ion channels preferentially controlling atrial repolarization (e.g., two-pore-domain K^+ -channels [7]), creating new opportunities to develop effective antiarrhythmic drugs with minimal ventricular side effects. Similarly, more information about signaling pathways regulating atrial electrophysiology and remodeling is becoming available. A prominent role for Ca^{2+} /CaMKII in AF was validated in animal studies and samples from patients with chronic AF [8]. However, due to its diverse functions in various tissues, novel, isoform-specific CaMKII inhibitors modulating Ca^{2+} /calmodulin regulation or targeting of CaMKII to its protein substrates will be needed to validate the anti-AF potential of CaMKII inhibition in clinical trials. Abnormal atrial metabolism and regulation of AMPK are also emerging contributors to the initiation and progression of AF [9], but their potential as antiarrhythmic targets requires further extensive investigation.

On the other hand, AF ablation was introduced without detailed understanding of molecular targets. However, optimizing the long-term success of ablation procedures necessitates insight into the structural and functional abnormalities promoting AF in an individual patient. Conceptually, AF can be maintained by repetitive ectopic activity and/or re-entry [1,5]. There has been a remarkable development in invasive and noninvasive imaging techniques to characterize the atrial substrate, resulting in procedures with improved long-term freedom from AF in some, but not all cohorts [3]. Nonetheless, it has proven challenging to definitively establish the mechanisms maintaining clinical AF [10] and consensus on the best ablation approach has not

yet been reached. Evidence for both re-entrant activity and abnormal impulse formation exists, but the methodological differences between mapping approaches and the extensive signal processing makes the interpretation of mapping recordings challenging, and impede a direct connection to AF mechanisms [3,11–12].

Besides further refinements at each individual scale, future research linking microscopic mechanisms and macroscopic mapping will be key to further optimize AF therapy.

• The etiology of AF patients is highly heterogeneous

Although classification of AF as paroxysmal, persistent or long-standing persistent has important prognostic implications, for example, with respect to the success of AF ablation [3], it neglects the diverse etiology of AF patients. AF can occur in the presence of a wide range of risk factors and comorbidities [1], each of which may differentially modulate the proarrhythmic substrate and clinical consequences of AF. For example, some studies suggest that women have more thromboembolic complications and less benefit from AF therapy, resulting in a higher AF-related morbidity and mortality, indicating potential gender-specific mechanisms [13]. Similarly, improved cardiorespiratory fitness has recently emerged as a potential key element in AF therapy in the setting of obesity [14]. These data are in line with an increasing importance of epicardial fat in AF pathophysiology [15]. However, the exact molecular mechanisms and applicability to other patient cohorts are unclear.

A better classification of AF will help to translate specific AF mechanisms to the appropriate clinical cohort, likely improving antiarrhythmic efficacy in clinical trials. Cellular electrophysiological differences between atrial cardiomyocytes from patients with paroxysmal and chronic AF have provided information on distinct molecular mechanisms that precede the arrhythmia, versus those that result as a consequence of AF [5]. However, even for a given AF type, there is substantial patient-to-patient variability in the clinical presentation, ranging from numerous short-lived AF episodes to few but long-lasting episodes, and from completely asymptomatic to severely symptomatic patients [1,5]. Different clinical presentations likely reflect distinct AF mechanisms. This heterogeneity of AF makes translation of generic AF mechanisms to patient therapy challenging, although recent advances in the characterization

“A better classification of atrial fibrillation will help to translate specific atrial fibrillation mechanisms to the appropriate clinical cohort, likely improving antiarrhythmic efficacy in clinical trials.”

of AF complexity may facilitate a more stratified approach. ECG biomarkers of AF complexity can predict long-term success of catheter ablation [16] and tailored therapy based on genetic information might also be possible and is currently being evaluated based on genetic variants near the *PITX2* gene [17]. Nonetheless, extrapolating genetic alterations to AF mechanisms in patients remains challenging. For example, both gain and loss of *PITX2* has recently been linked to increased AF risk, albeit through distinct mechanisms [18]. Moreover, there is very little information available about the influence of individual risk factors (e.g., heart failure or diabetes) on human atrial electrophysiology, calcium handling and related atrial remodeling.

• **Currently available preclinical models have important limitations**

Preclinical models play a key role in the development of new mechanistic insights and will be indispensable to obtain disease-specific stratification of AF therapy [5,6]. Animal models allow a better control of clinically relevant variables and comorbidities and enable multiscale studies by correlating *in vivo* and *in vitro* manifestations in the same animal. However, translation of findings from animal models to patients has proven challenging [19]. Among other things, most animal models do not show spontaneous AF initiation and subsequent progression, instead relying on burst pacing to assess substrate vulnerability. Similarly, the timecourse of disease is significantly shorter than in humans, likely affecting AF pathophysiology. Although human atrial samples reflecting the full disease complexity are available for preclinical investigations, they are generally limited to the right-atrial appendage and only available from patients undergoing open heart surgery, which is not representative for the majority of AF patients [5,6].

Emerging preclinical models, such as patient-specific induced pluripotent stem cell-derived cardiomyocytes and computational modeling might help to refine arrhythmogenic mechanisms by bridging the divide between species and scales [20], although such approaches also have limitations that need consideration [6,20]. A careful combination of experimental approaches is likely needed to establish fundamental AF-promoting mechanisms under well-defined conditions, develop tailored therapy for specific molecular targets and evaluate them in well-characterized clinical cohorts.

• **Limited understanding of structural remodeling & potential upstream therapy**

Current pharmacological approaches have mainly focused on inhibition of cardiomyocyte ion channels. Atrial structural remodeling, notably fibrosis, plays a major role in AF progression [21]. Increased atrial fibrosis is associated with increased duration of pacing-induced AF in animals, and slow heterogeneous conduction resulting from fibrosis is an established re-entry-promoting mechanism [1,5,21]. Although atrial fibrosis was associated with increased AF recurrence rate [21], overall fibrosis levels poorly correlate with AF complexity [22]. The molecular processes controlling fibroblast function, proliferation, differentiation and the bidirectional fibroblast-cardiomyocyte regulation remain unclear, limiting the success of upstream therapy aimed to prevent progressive AF-promoting remodeling. The latter strongly affects fibroblast proliferation and differentiation [23] and alters fibroblast ion channel function in AF patients [24,25], but the physiological relevance and the pathways linking fibroblast ion channel function to fibrogenesis and eventually to cardiomyocyte dysfunction are largely unknown.

Conclusion & future perspective

Technological and scientific innovations have greatly enhanced our understanding of AF mechanisms, which has already impacted clinical AF management. Nonetheless, many challenges remain. The diversity of clinical conditions and pathophysiological processes regulating AF likely preclude a 'one-size-fits-all' therapy. Thus, a close collaboration between basic scientists, cardiologists, cardiothoracic surgeons, engineers, industry and regulatory authorities is needed to overcome the translational challenges and establish more tailored AF therapies. Recent developments are encouraging, suggesting that such approaches are indeed possible.

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