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PREDICTIVE MALE-TO-FEMALE TRANSLATION OF CARDIAC ELECTROPHYSIOLOGICAL RESPONSE TO DRUGS

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Abstract

Despite evidence that women are at higher risk of drug-induced Torsade de Pointes and sudden cardiac death, female sex is vastly underrepresented in cardiovascular research, thus limiting our fundamental understanding of sex-specific arrhythmia mechanisms and our ability to predict arrhythmia propensity. To address this urgent clinical and preclinical need, we developed a quantitative tool that predicts the electrophysiological response to drug administration in female cardiomyocytes starting from data collected in males. We demonstrate the suitability of our translator for sex-specific cardiac safety assessment and include proof-of-concept application of our translator to *in vitro* and *in vivo* data.

Keywords

Introduction

Sex differences in cardiovascular physiology have gained increasing attention in recent years, with growing evidence indicating that males and females differ in various aspects of their cardiovascular function. At the cardiomyocyte level, sex differences in action potential (AP) and Ca^{2+} handling characteristics have been reported, which can contribute to sex-specific variations in cardiac arrhythmia susceptibility and response to treatment. For example, female sex is an independent risk factor for both inherited and acquired (e.g., drug-induced) Long QT syndrome and Torsade de Pointes (TdP) [1]. Many drugs have been found to elevate the risk of TdP [1], especially in women. While these drugs have been approved and put on the market after extensive testing, it is important to note that both fundamental and clinical studies have historically focused mainly on males [1–4], with the

mechanistic bases and implications of sex-specific differences in females remaining largely unexplored.

The Clancy group developed mathematical models that recapitulate *in silico* male and female ventricular human heart cells by incorporating experimentally-determined genomic differences and effects of sex steroid hormones into virtual myocytes (2), and investigated the sex-specific mechanisms of arrhythmia. Recently, our team updated these sex-specific models and integrated a machine learning-based classifier to categorize TdP risk associated with various drugs in both males and females (1). Our investigation exposed the need for distinct biomarkers to classify the risk in each sex and revealed possible sex disparities in the categorization of moderate-risk drugs. Specifically, we found that some drugs that were deemed safe for male showed indications of harm in female, and that adoption of male-biased metrics can lead to a systematic underestimation of torsadogenic risk in female (1). To facilitate evaluation of the impact of sex differences on cardiomyocyte function and arrhythmogenesis, we utilized our recent cross-species translator (5) to developed quantitative tools that predict the electrophysiological response to perturbations/stressors (including drug administration) in female cardiomyocytes starting from data collected in males.

Development of the cross-sex translator

Using mathematical models of excitation-contraction coupling in male and female human ventricular myocytes (1,2) and an established population of models approach (6,7), we generated populations of 5,000 model variants by randomly perturbing baseline model parameters (Fig. 1A, *left*). These modeling frameworks have proven powerful for studying mechanisms underlying physiological variability in cardiac electrophysiology and pro-arrhythmic risk (8). We extracted AP and Ca^{2+} transient (CaT) properties (e.g., APD_{90}, CaT_{amp}) in each model variant paced to steady-state (and collected their log-transformed values in the matrices F_{male} and F_{female}). We applied multivariable linear regression to these matrices using a nonlinear iterative partial least squares algorithm, and obtained the "cross-sex translator" B_{cross}, i.e., a set of regression coefficients mapping male features (F_{male}) onto female electrophysiology (F_{female}) and vice versa (Fig. 1A, *right*). B_{cross} is such that the product of the input features (i.e., F_{male}) and B_{cross} approximates the output features (i.e., F_{female}). By utilizing the matrix B_{cross}, one can predict the values of AP and CaT features in the "output" sex based on the values of these features in the "input" sex. Each output feature can be calculated by multiplying each input feature by its corresponding regression coefficient.

Source code and documentation are freely available at http://elegrandi.wixsite.com/grandilab/downloads and https://github.com/drgrandilab.

Fig. 1B shows a cross-species translator built using 10 simulated biomarkers in both male and female and Fig. 1C demonstrates the application of our translator to simulated control male data (steady-state simulations at 1-Hz pacing rate): the male-to-female translated biomarkers (*circles* and *white bars*) show good agreement with those extracted from the control female simulations (*blue lines* and *bars*). This is also evident in the cross-validation

performed with an independent set of simulated data, obtained with a new population of 400 models, and comparing the values predicted by the translator vs. the actual (simulated) values (Fig. 1D). Indeed, the translator accurately predicts the longer APD and decreased CaT amplitude in female vs. male (Fig. 1C). Of note, the translation of each biomarker depends heavily on its counterpart in the opposite sex (Fig. 1B), which implies that the translator can maintain accuracy with fewer biomarkers, i.e., APD data in female could be predicted from APD data in male without information on other biomarkers (*not shown*).

Male-to-female translation of drug responses

We further validated our translator against an independent simulated data set describing the effects of a large group of 95 drugs (1) on the baseline male and female models. For example, in Fig. 2A the biomarkers extracted from simulating administration of dofetilide in the male models were translated into female biomarkers. The translated biomarkers were remarkably similar to those obtained from simulating the female model response to dofetilide, thus confirming the efficacy of the translator. For each drug, we generated a rich dataset by simulating multiple [drug] equal to 1x, 2x, 3x, 4x the effective therapeutic plasma concentration (ETPC) and various pacing rates (0.5, 1, 2 Hz). Representative AP and CaT traces corresponding to male and female responses to all drugs (at a concentration corresponding to their ETPC) at 1-Hz pacing rate are shown in Fig. 2B, *top*. We tested the predictive ability of our B_{cross} in translating the male simulations into female responses. Results at increasing drug concentrations (at 1-Hz pacing rate) are in Fig. 2B, *bottom* and overall show high accuracy of prediction of drug-induced effects on female AP and CaT, where the average discrepancy between predicted and actual biomarkers falls within 1-2% for all the drugs included in the dataset. We did encounter rare cases of higher error, which generally seems to increase with higher drug concentration. This is for example the case of extreme drug-induced APD prolongation, e.g. bepridil (200% APD_{90}, male control vs. male drug) at 4x ETPC, where the relationship between APD and underlying model parameters may be further from the linear regime that the regression model is based on. We also excluded from the analysis 3 drugs that showed EADs at concentrations >= 2x, 3x, or 4x (ibutilide, thiorazine and quinidine, respectively). In these cases, we did not generate translators (with ibutilide, EADs occur both in male and female models) or could not validated them (with quinidine and thiorazine, only the female model exhibits EADs), as not all the features could be computed. Future work should address strategies to overcome this limitation, for example employing translators built on a subset of features. Nevertheless, it is worth noting that, out of the 95 drugs tested, 90 had a translation error below 3% at 4x ETPC.

We next used our "male-to-female" translated features as inputs into our previously developed female-specific classifier of drug-induced torsadogenic risk (1) to test the suitability of our translator for cardiac safety assessment in women. We simulated the drugs' effects in the male model and applied the translator to predict the four TdP risk-associated female biomarkers identified in our previous study, i.e., CaT_{tau} (0.5-Hz, 3x and 4x ETPC [drug]), CaT integral (2-Hz, 4x ETPC [drug]) and CaT_{min} (0.5-Hz, 4x ETPC [drug]) (1). Using the classifier performance obtained with simulated data as input features as a

benchmark, Fig. 2C shows that the translator can closely recapitulate the results from our previous publication, thus providing additional validation for the translator.

While the availability is scarce, we endeavored to validate the cross-sex translator against experimental (APD) and clinical (QTc) data (Fig. 2D). We generated a new translator with only one biomarker, simulated ADP_{90} at 1-Hz pacing rate, to serve as a proxy for both APD and QTc. We gave in input to the translator the experimentally measured mean changes in male QTc in response to a quinidine concentration corresponding to its ETPC (8). The translator predicted a drug-induced 7% increase in the female APD_{90}, compared with the 10±1% (mean and STD) QTc prolongation seen clinically in females after administration of quinidine (9). Using the same translator, we also compared application of a dofetilide concentration close to its ETPC in inducible pluripotent stem cell derived cardiomyocytes (iPSC-CMs). When inputting the dofetilide-induced 20% APD_{90} prolongation in male myocyte experiments (10), our translation predicted a drug-induced 17% change in female APD_{90} vs. 10±10% reported experimentally (10).

Conclusions

The issue of underrepresentation of female data in the cardiovascular literature is not a recent one. Despite being a long-standing concern, improvement has been marginal in the past decade (3,4). Our findings suggest that the translator can serve as a powerful tool in bridging the knowledge gap between male and female cardiovascular responses to drugs. It has the potential to uncover novel insight from previously recorded data and represents a significant step toward attenuating sex disparities in medicine. Indeed, the utilization of a cross-sex translator in analyzing cardiac electrophysiological responses to medications holds promise in identifying disparities in drug effectiveness and safety between males and females, thus enhancing the development of new drugs and optimizing existing therapies. Specifically, by enabling the translation of electrophysiological data across sexes, the translator could improve accuracy of cardiac safety assessment in females, who are currently underrepresented in cardiovascular research studies and clinical trials. However, this tool should not be regarded as a substitute for conducting new experiments on both sexes, but rather viewed as valuable aid in confirming and supplementing the findings of such experiments. Instead, our study underscores the importance of considering sex as a fundamental biological variable in both fundamental and clinical research design. Deciphering the differential impact of drugs on cardiac electrophysiology in males and females might enable healthcare practitioners to personalize treatment plans based on the patient's sex, potentially yielding improved outcomes, and minimizing adverse effects.

Sources of Funding:

Nonstandard Abbreviations and Acronyms

AP   Action Potential

AP$_{amp}$	Action Potential Amplitude
APD$_{xx}$	Action Potential Duration to XX% of repolarization
CaT	Calcium Transient
CaT$_{amp}$	Calcium Transient Amplitude
CaT$_{min}$	Diastolic Calcium Concentration
CaT$_{t50}$	Calcium Transient time to 50% decay
CaT$_{tau}$	Calcium Transient decay time constant
CaT$_{ttp}$	Calcium Transient time to peak
ETPC	Effective Therapeutic Plasma Concentration
iPSC-CMs	Inducible Pluripotent Stem Cell derived Cardiomyocytes
MDP	Maximum Diastolic Potential/Resting Membrane Potential
TdP	Torsade de Pointes
UV	Upstroke Velocity

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Clinical Perspective

COMPETENCY IN MEDICAL KNOWLEDGE:

The development of a male-to-female translator will facilitate the evaluation of the impact of sex differences on cardiomyocyte function and arrhythmogenesis. This will improve our understanding of sex-specific mechanisms underlying arrhythmias and our ability to predict arrhythmia propensity, which could advance the field of cardiac electrophysiology research more broadly. Indeed, the male-to-female translator represents a significant technological advancement that may have broader applications beyond the study of arrhythmia mechanisms and drug safety assessment, potentially leading to new insights into the sex-specific mechanisms underlying other cardiovascular diseases.

TRANSLATIONAL OUTLOOK:

The cross-sex translator of cardiac electrophysiological responses to drugs could help to identify potential differences in drug efficacy and safety between males and females, which could improve the development of new drugs and the optimization of existing therapies. The ability to translate electrophysiological data across sexes will improve the accuracy of cardiac safety assessment in females, who are currently underrepresented in cardiovascular research studies and clinical trials. This will lead to better identification and management of e.g., torsadogenic risk in females and ultimately improve drug safety for all patients. Nevertheless, it is important to emphasize that the cross-sex translator cannot substitute experimentation. On the contrary, our study suggests that it is imperative to consider sex as a biological variable in both fundamental and clinical research design. By understanding how drugs affect cardiac electrophysiology differently in males and females, clinicians may be able to tailor treatment plans to individual patients based on their sex, potentially improving outcomes and minimizing side effects.
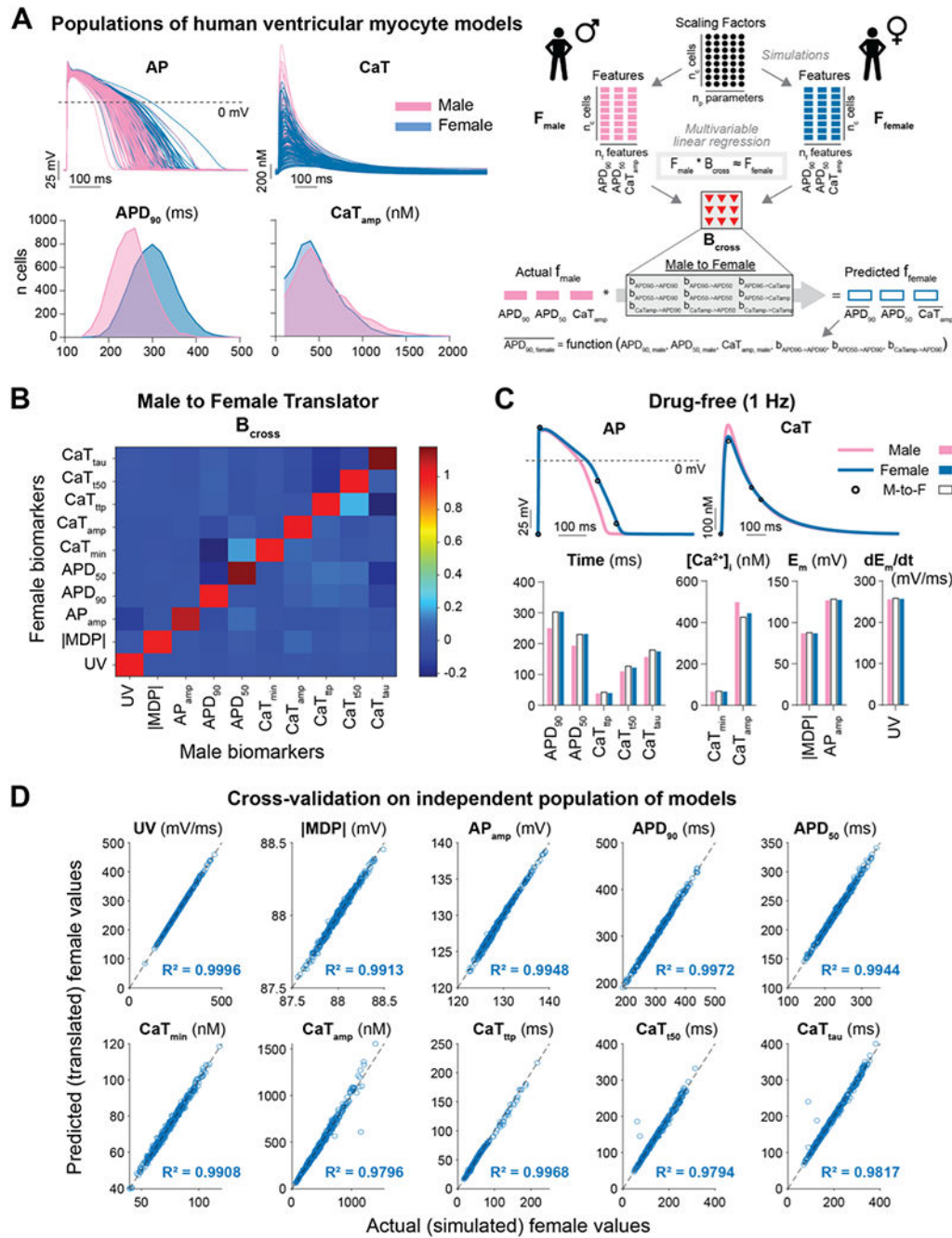
Fig. 1: Development and cross-validation of a cross-sex translator of cardiac electrophysiology.
A, *left* Populations of male and female cardiomyocyte action potentials (APs) and
Ca^{2+} transients (CaTs) were created by randomly perturbing selected parameters in the
baseline models,(1,2) as in (5). Distribution of AP duration (APD) and CaT amplitude
are displayed for the male and female populations. *Right,* In each population, AP and
CaT features (squares) are estimated at steady-state in each model variant, and their
values are log-transformed and collected in the matrices F_{male} and F_{female}. We generate
the cross-sex translator B_{cross} by applying multivariable linear regression to F_{male} and

F_{female}. Regression coefficients in B_{cross} (triangles) are used to predict AP and CaT features in the output species (array "predicted f_{female}"), given the values observed in the input species (array "actual f_{male}"). **B,** For demonstration, we generated a translator based on 10 electrophysiologic biomarkers. The B_{cross} is shown, whereby the color-coded regression coefficients indicate the contribution of each male biomarker in predicting the female biomarker. **C,** Waveform of simulated male and female AP and CaT (top) and extracted biomarkers (bottom) are compared with male-to-female translated biomarkers (circles on top and white bars on bottom) in baseline conditions. **D,** Scatter plots show the result of cross-validation performed with an independent set of simulated data, obtained in different populations of 400 models. For each biomarker, the values predicted by the translator are plotted against the actual (simulated) values, and the coefficient of determination R^2 is reported.
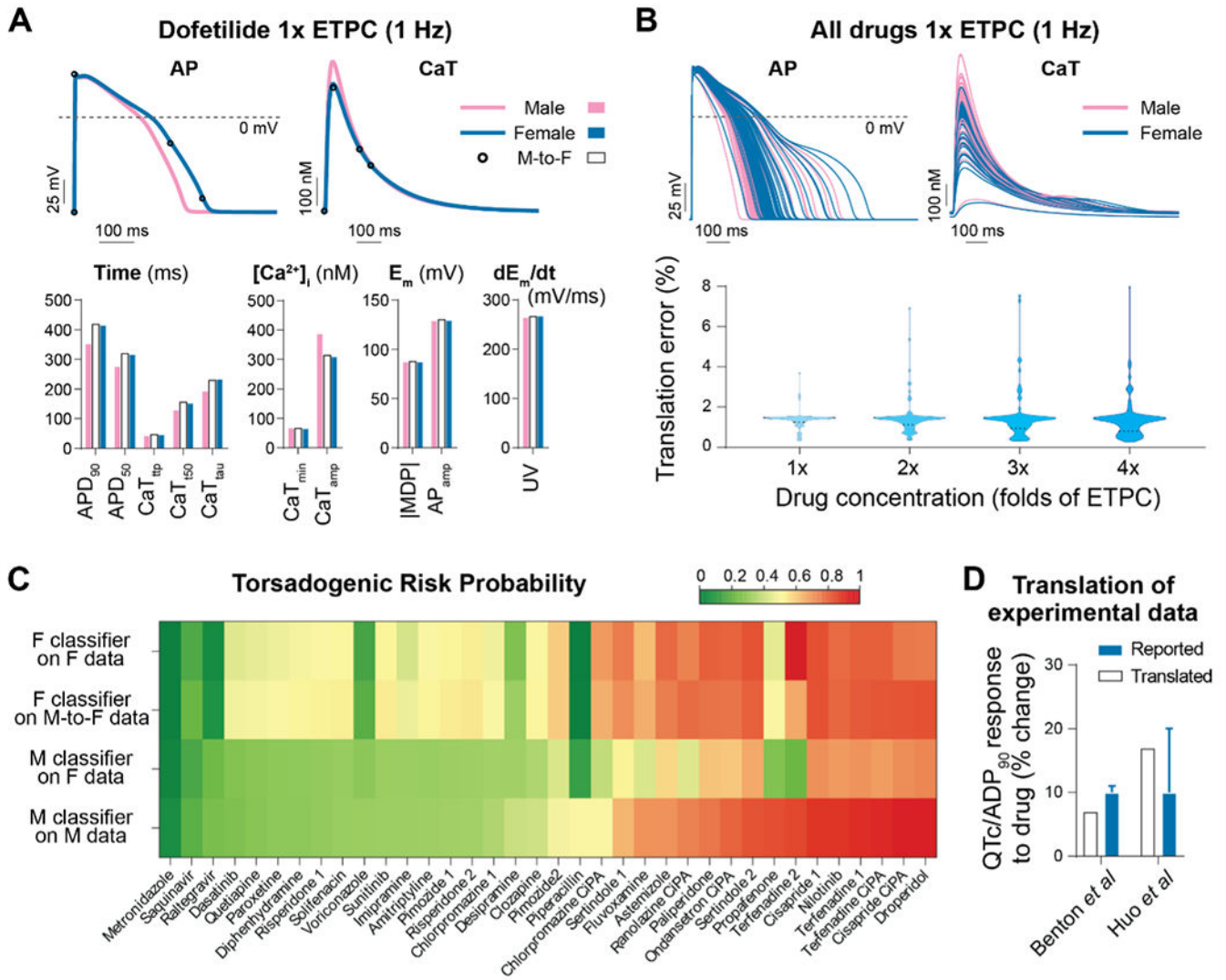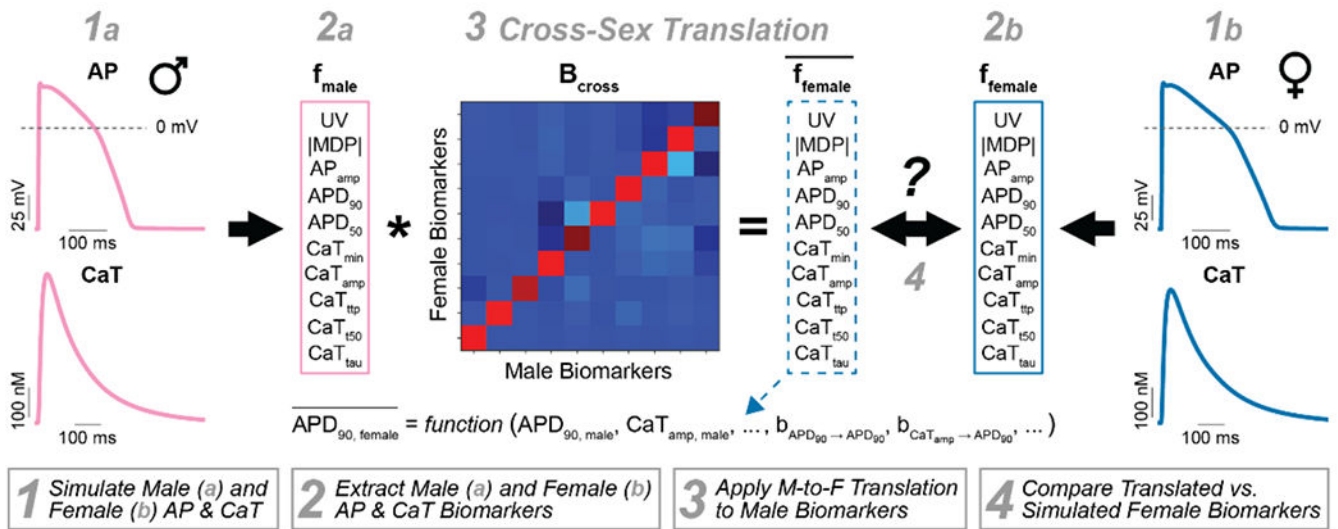
Fig. 2: Application of the male-to-female translator to predict drug response.
A, Waveform of simulated male and female AP and CaT (top) and extracted biomarkers (bottom) are compared with male-to-female translated biomarkers (circles on top and white bars on bottom after application of dofetilide. **B,** *top* simulated effects of 95 drugs (at a concentration equal to their ETPC) on the AP and CaT with male (blue) and female (magenta) biophysical myocyte models paced at 1 Hz. ***Bottom,*** violin plot depicting the relative male-to-female translation error at various drug concentrations. Errors are calculated as the average of those calculated for each biomarker abs(1-predicted value/actual value). **C,** Translated females biomarkers were used with a machine learning-based classifier of torsadogenic risk.(1) The risk prediction using male-to-female translated biomarkers as the input resembles that obtained when using simulated female features. **D,** Male-to-female translated experimental data are compared with *in vivo* QTc and *in vitro* APD changes following administration of quinidine and dofetilide in patients and iPSC-CMs respectively.

Central Illustration: Male-to-female translator of cardiac electrophysiology.
The flowchart shows simulation of AP and CaT in a male-like (*1a*) and a female-like (*1b*) model and features extraction (*2a* and *2b*) used to generate the translator B_{cross} through multivariable linear regression. Inputting male AP/CaT biomarkers into the translator yields female-like AP/CaT biomarker predictions (3), which are compared to the results from simulations of the female-like AP model (4).