ABSTRACT FACE PAGE

1. **Presenting Author's name: _____Chiara Campana_____**
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5. **Presenting Author's gender (optional): _____female_____**
6. **Presenting Author's race (optional): _____**
7. **Presenting Author's ethnicity (optional): _____**
8. **Presenting Author's affiliation sector: (check one or more)**
   - ✔ Academia
   - ○ Industry
   - ○ Federal Employee/Contractor
   - ○ Private Foundation
   - ○ Other: _____
9. **Presenting Author's Career stage: (check one)**
   - ○ K-12 student
   - ○ Undergraduate student
   - ✔ Graduate Student
   - ○ Post-doctoral Trainee
   - ○ Young employee (within first 3 year of post-training position)
   - ○ Mid-level employee (3-10 years of post-training position)
   - ○ Senior-level employee (10+ years of post-training position)
   - ○ Other: _____
10. **Website / twitter handle / other public links (optional): _____**
11. **Is this the research presented in this abstract supported by IMAG MSM-related U01 funding? Yes or No**
12. **If the Presenting Author is a trainee, who is the trainee's primary research advisor? __Eric A. Sobie _____**

TRAINEE POSTER AND ORAL PRESENTATION COMPETITONS:

New to the meeting this year, we are holding *both* a trainee poster competition and a trainee oral presentation competition! If the presenting author is a trainee (i.e., a student at any level or a post doctoral trainee), he/she may enter his/her abstract in the trainee poster competition, the trainee oral presentation competition, or both competitions. Trainees may also submit more than one abstract to the meeting and enter more than one abstract in these competitions. Prizes will be given to the presenters of the top-ranked trainee oral presentation and the top-ranked trainee poster (judged during the meeting by the Program Committee).

13. **If the Presenting author is a trainee, would the Presenting Author like to enter his/her abstract in the Trainee Poster Competition*? Yes or No**

*Note: Trainees who enter the poster competition are expected to stand by their poster during the scheduled poster sessions and present them to the judges.

14. **If the Presenting author is a trainee, would the Presenting Author like to enter his/her abstract in the Trainee Oral Presentation Competition**? Yes or No**

**Note: The Program Committee will select the top four abstracts from trainees who elect to enter their abstract into the trainee oral presentation competition, these four trainees will be notified by Feb. 17th, and they will deliver their oral presentations (which will be judged) on the second day of the meeting after lunch.

A DISTINCT MOLECULAR MECHANISM BY WHICH PHENYTOIN RESCUES A NOVEL LONG QT 3 VARIANT

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BACKGROUND: Genetic variants in SCN5A can result in channelopathies such as the long QT syndrome type 3 (LQT3), but the therapeutic response to Na^+ channel blockers can vary. We reported a case of an infant with malignant LQT3 and a missense Q1475P SCN5A variant, who was effectively treated with phenytoin, but only partially with mexiletine. Here, we functionally characterize this variant and investigate possible mechanisms for the differential drug actions.

METHODS: Wild-type or mutant $Na_v1.5$ cDNAs were examined in transfected HEK293 cells with patch clamping and biochemical assays. We used computational modelling to provide insights into altered channel kinetics and to predict effects on the action potential.

RESULTS: The Q1475P variant in $Na_v1.5$ reduced the current density and channel surface expression, characteristic of a trafficking defect. The variant also led to positive shifts in the voltage dependence of steady-state activation and inactivation, faster inactivation and recovery from inactivation, and increased "late" Na^+ current. Simulations of $Na_v1.5$ gating with a 9-state Markov model suggested that transitions from inactivated to closed states were accelerated in Q1475P channels, leading to accumulation of channels in non-inactivated closed states. Simulations with a human ventricular myocyte model predicted action potential prolongation in cells with Q1475P, compared with wild type, channels. The patch clamp data showed that mexiletine and phenytoin similarly rescued some of the gating defects. Chronic incubation with mexiletine, but not phenytoin, rescued the $Na_v1.5$-Q1475P trafficking defect, thus increasing mutant channel expression.

CONCLUSIONS: The gain-of-function effects of $Na_v1.5$-Q1475P predominate to cause a malignant long QT phenotype. Phenytoin partially corrects the gating defect without restoring surface expression of the mutant channel, whereas mexiletine restores surface expression of the mutant channel, which may pose a proarrhythmic risk. Our data makes a case for functional studies before embarking on a one-for-all gene-specific therapy regime of arrhythmias.