Understanding the mechanisms of hERG channel gating and drug inhibition using cryo-EM

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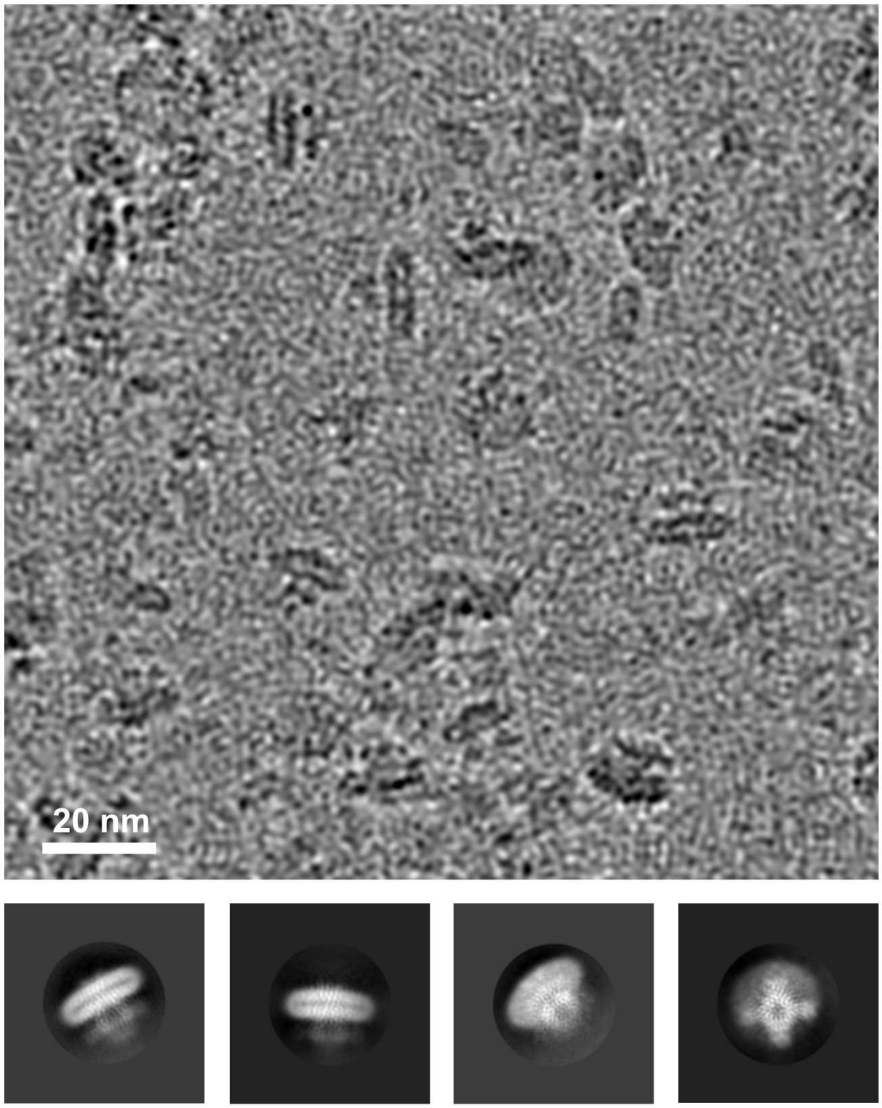
The *human ether-a-g-o-go related gene* (hERG) potassium ion channel carries the major repolarizing current in the cardiac action potential. Loss-of-function mutations in the hERG K^+ channel result in prolongation of the cardiac QT interval and increase the risk of life threatening cardiac arrhythmias such as torsade de pointes. In addition, these arrhythmias can be caused by drug blockade of the ion conduction pathway which reduces the repolarizing current. The first cryo-EM structure of the hERG K^+ channel was published in 2017 (Wang & MacKinnon, 2017). However, much of the molecular details of gating and drug binding remain unknown. To further elucidate the mechanism of channel gating and drug inhibition of the hERG potassium ion channel we have purified hERG protein constructs that contain point mutations to stabilise different major gating states of the channel. Preliminary cryo-EM map (typical micrograph and 2D class averages shown in the Figure) shows major domains are present and consistent with the published structure. We are also currently investigating the use of nanodiscs to further stabilise the channel to achieve better resolution.



Wang W, MacKinnon R. (2017). Cryo-EM structure of the open human ether-à-go-go-related K^+ channel hERG. *Cell* ***169****: 422-43.*

C. Lau and M. Hunter contributed equally to this work.