

1. Record Nr.	UNINA9910779277703321
Autore	Killeen Matthew J
Titolo	Cardiac drug safety [[electronic resource]] : a bench to bedside approach / / Matthew J. Killeen
Pubbl/distr/stampa	Singapore, : World Scientific Pub. Co., 2012
ISBN	1-280-66922-5 9786613646156 981-4317-46-2
Descrizione fisica	1 online resource (189 p.)
Disciplina	363.738/74 363.73874 615.71
Soggetti	Cardiovascular agents
Lingua di pubblicazione	Inglese
Formato	Materiale a stampa
Livello bibliografico	Monografia
Note generali	Description based upon print version of record.
Nota di bibliografia	Includes bibliographical references and index.
Nota di contenuto	Contents; Foreword; "Et causae quoque aestimatio saepe morbum solvit" [Celsus: Prooemium 69, De Medicina]; Preface; Chapter 1 Challenges Facing the Pharmaceutical Industry in the 21st Century; Introduction; The Impact of Cardiac Toxicity on the Pharmaceutical Industry; References; Chapter 2 The Cellular Basis of Cardiac Electrophysiology; Introduction; The Initiation of the Heart Beat; The Ventricular Cardiac Action Potential; The Relationship Between the Cardiac Action Potential and the Electrocardiogram; Ion Channels Underlying the Cardiac Action Potential; Sodium channels; Calcium channels; Potassium channels; Cardiac potassium channels; The transient outward potassium channel; Delayed rectifier potassium channels; The ultra rapid delayed rectifier potassium channel; The HERG potassium channel; The slowly activating delayed rectifier potassium channel; Inwardly rectifying potassium channels; Species-dependent variability of potassium channels; Potassium channel subunits; Summary; References; Chapter 3 Clinical Arrhythmia Syndromes; Introduction; The Long QT Syndrome; Congenital Long QT Syndrome; Drug-Induced QT Prolongation; Summary; References; Chapter 4 The Mechanisms Underlying Cardiac Arrhythmias

Introduction; Mechanisms Underlying Cardiac Arrhythmias; Abnormal Automaticity; Early and Delayed After depolarizations; Re-entry; Transmural Dispersion of Repolarization; How does Action Potential and QT Prolongation Generate Arrhythmias?; Does the M-Cell Play a Role in Arrhythmia Induction in Humans?; Using Mouse Models to Study Arrhythmia Mechanisms; Experimental Studies Exploring the Relationship Between Changes in Transmural Repolarization Gradients and Arrhythmias in Mouse Hearts

Arrhythmia Mechanisms and Novel Antiarrhythmic Approaches Identified Using the Hypokalemic Mouse Model Summary; References; Chapter 5 The Mechanisms Underlying Drug-Induced Arrhythmias; Introduction; The Classical Model of Drug-Induced QT Prolongation and Proarrhythmia: HERG Blockade; Additional Mechanisms Contributing to Drug-Induced Arrhythmias; Drug-Induction Activation of Depolarizing Ion Channels; Drug-Induced Changes in Ion Channel Expression; Drug-Induced Sodium Channel Dysfunction; Summary; References; Chapter 6 Assessing Cardiac Safety in Drug Development; Introduction Preclinical Evaluation of Cardiac Drug Safety The ICH S7B Guidelines; Single Cell Safety Studies; The Purkinje Fiber Model; The Ventricular Wedge Model; Isolated Heart Models; In Vivo Models; The Impact of Species-Related Differences in Cardiac Electrophysiology on Preclinical Drug Safety Assessment; Methods to Provoke Arrhythmias in Preclinical Studies; Programmed electrical stimulation; Reductions in the extracellular K<sup>+</sup> concentration; Clinical Evaluation of Cardiac Safety; The Thorough QT study; Thorough QT study design; Additional Biomarkers to Detect Drug-Induced Proarrhythmia

Variability of repolarization

---

#### Sommario/riassunto

Ensuring the safety of new medical products remains a major challenge for the pharmaceutical industry. Cardiac safety, particularly drug-induced heart rhythm abnormalities, remains an important cause of pipeline attrition and has resulted in countless major product recalls or label changes. The risk of encountering this major adverse event continues to shape the drug development and regulatory landscape. Extensive research over the past decade has shed light on the root causes of arrhythmias that are triggered by medications and has helped drive, and optimize, drug safety testing. However,

---