

# Increased risk of Torsades de Pointes in streptozotocin-induced diabetic rats.

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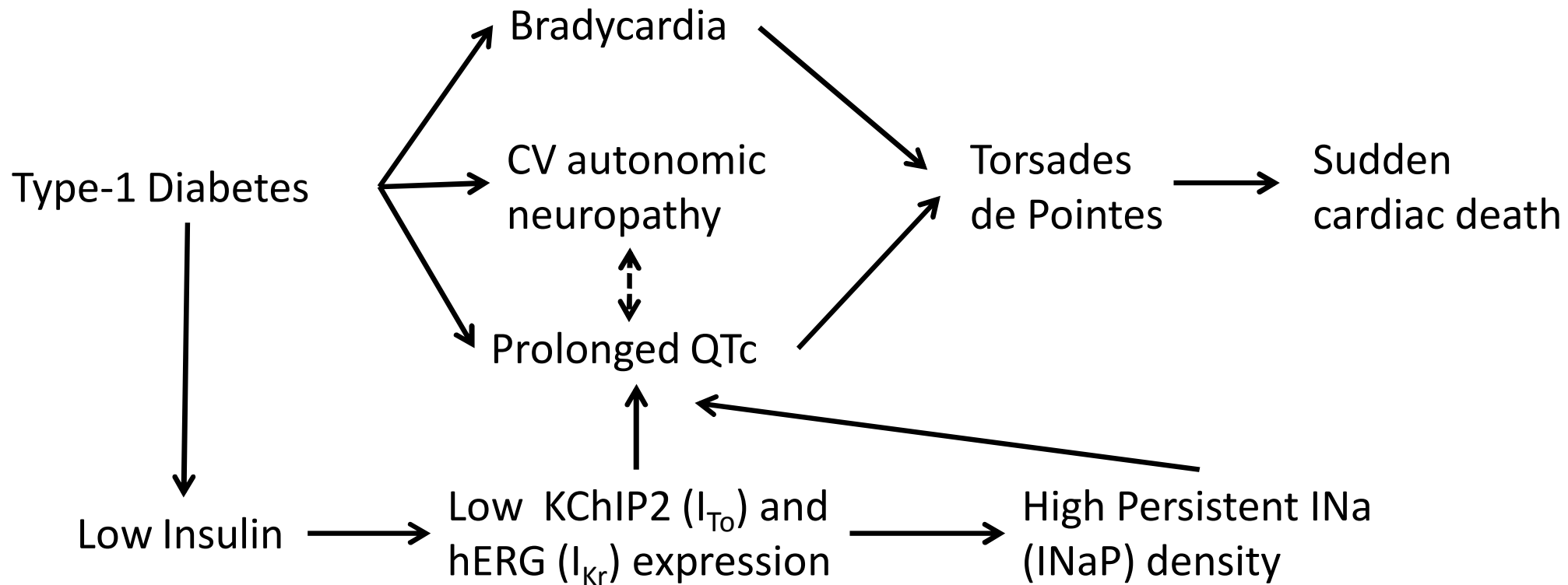
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# Long QT in diabetic patients



Why are diabetic patients at greater risk of sudden cardiac death?

- QTc prolongation is present in 9-16% of type-1 diabetic patients.
- Diabetic autonomic neuropathy is frequent;
- Humans with autonomic system disorders/impairments are more susceptible to drug-induced QTc prolongation

# The project

- Rationale

With a reduced repolarisation reserve, human diabetic patients may not be adequately represented in our current cardiac safety models.

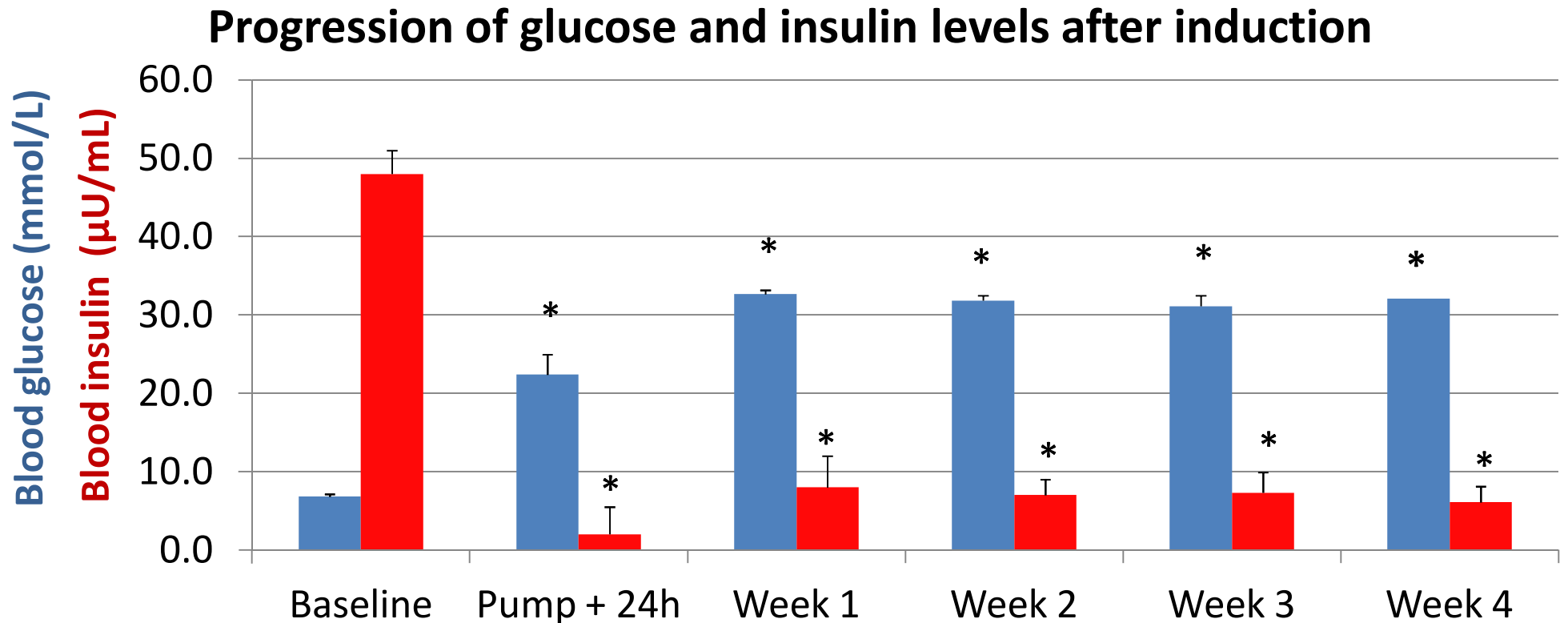
- Purpose

1. To characterize the extent, timing, and potential causes of QTc prolongation in a type-1 diabetic rat model
2. To confirm that this type-1 diabetic model exhibited enhanced sensitivity to drug-induced QTc prolongation
3. To test a novel compound with a potential novel mechanism of drug-induced LQTc mitigation

# Induction of type-1 diabetes

- Adult male Sprague-Dawley rats
- One 45 mg/kg iv injection of streptozotocin on Day 1
- Day 3: Implantation of subcutaneous osmotic pumps filled with slow insulin formulated in proprietary stabilization buffer: 2 units per day delivered for 30 days
- The animals were fed normal rat chow *ad libitum*
- Daily glycaemia tests, clinical signs assessment; weekly insulin tests and ECG recordings under isoflurane anesthesia prior and after induction
- Drug-induced QTc challenges on Day 30:
  - 3 mg/kg crizotinib (lung carcinoma)
  - 4 mg/kg nilotinib (myelogenous leukemia)
  - i.v. injections followed by 30+ minutes of recording

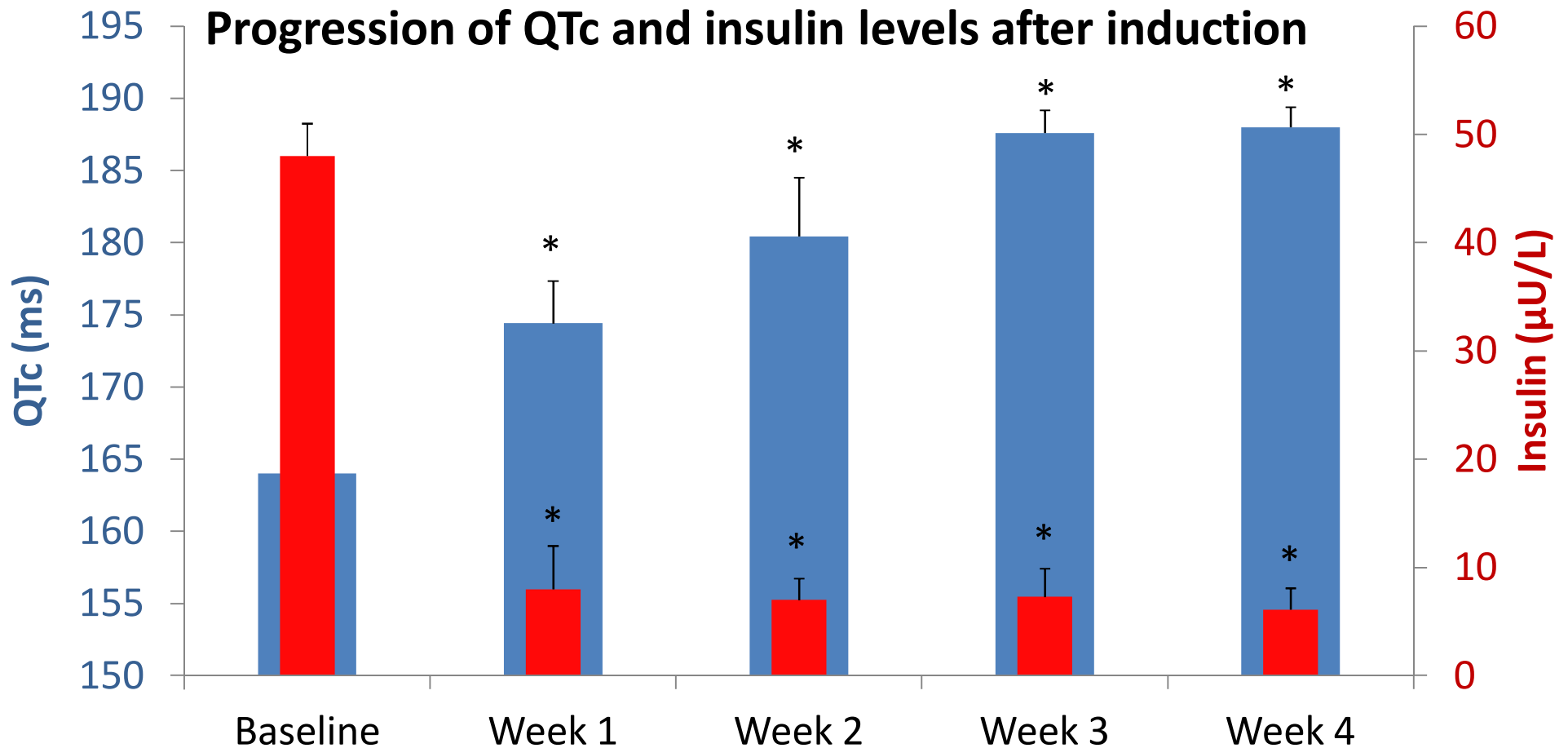
# Progression of the disease: Insulin and glycaemia



Glucose: OneTouch Verio IQ

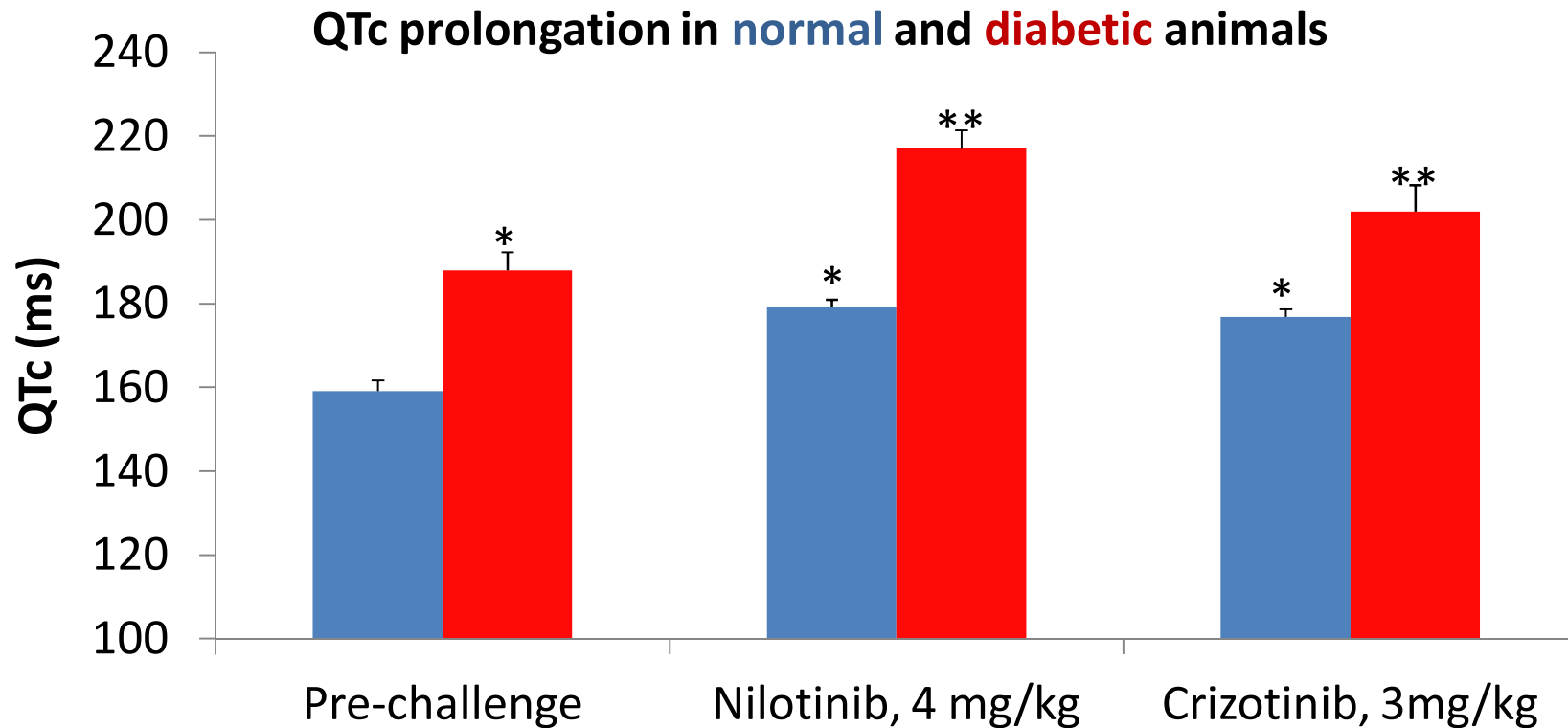
Insulin: Abcam ELISA

# Progression of the disease: QT prolongation



As expected, the kinetics of hypoinsulinemia appear faster than those of QTc prolongation. Yet QTc is statistically increased after only 1 week, levels off after 3 weeks post-induction

# Decreased repolarisation reserve



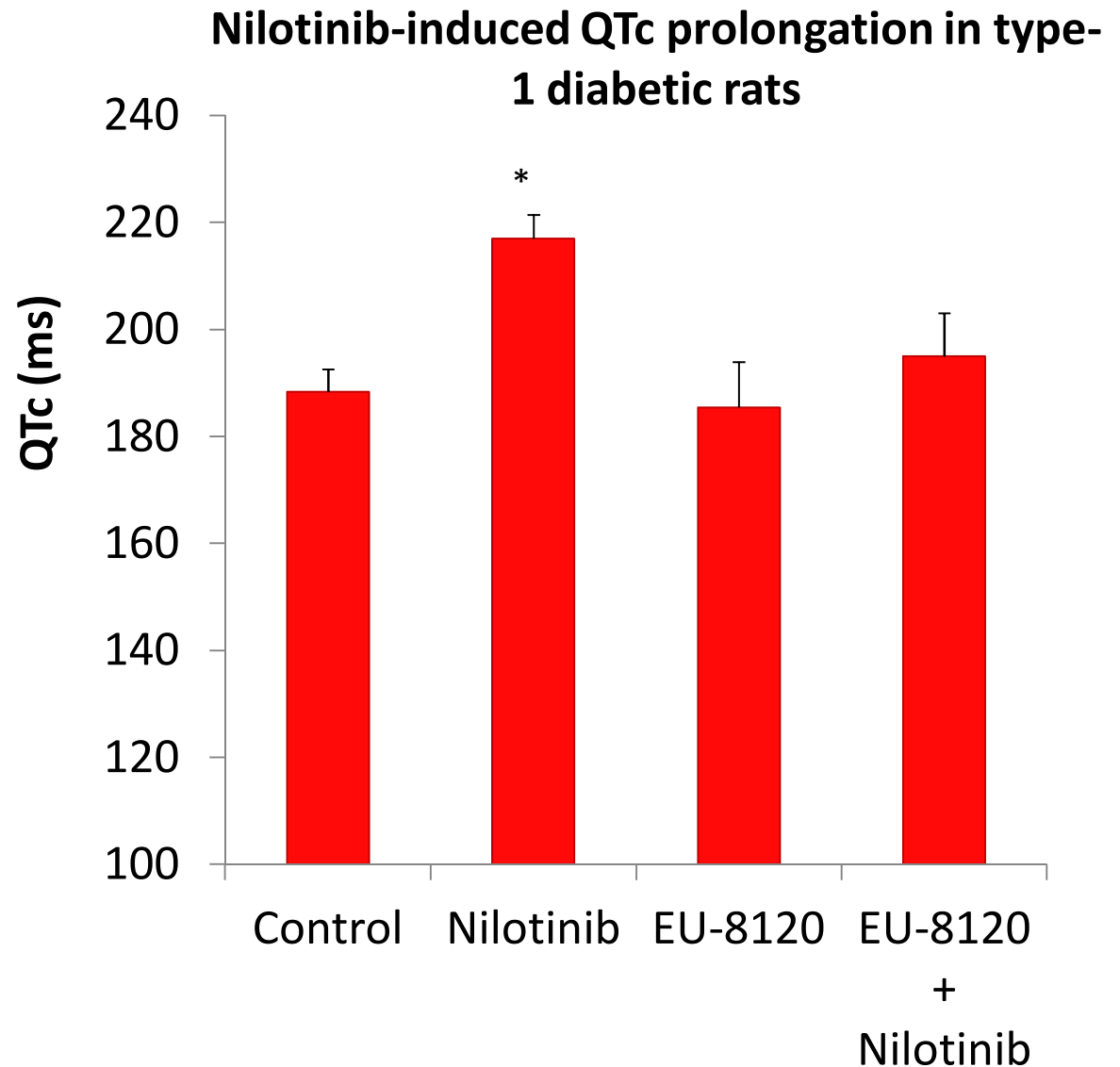
Nilotinib: Tyrosine kinase inhibitor for the treatment of chronic myelogenous leukemia

Crizotinib: anaplastic lymphoma kinase inhibitor, for the treatment of non-small cell lung cancer.

For both these compounds, QTc prolongation is one of the dose-limiting toxicities.

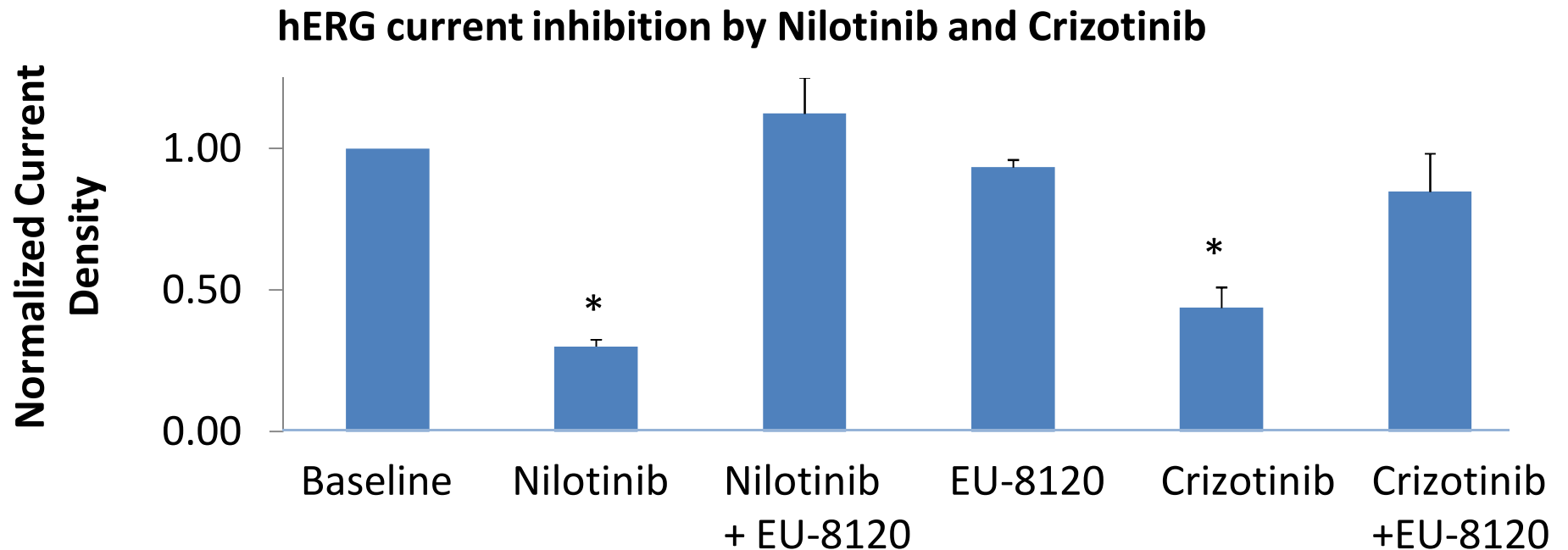
# Mitigation of QT prolongation: EU-8120

- **EU-8120**: A proprietary eutectic blend of phospholipids and fatty acids
- By itself, does not revert the diabetic-induced LQTc
- Shown to have IKr/hERG current -salvaging properties
- Currently in clinical development: it mitigates dose-limiting cardiovascular toxicity and opens the therapeutic window for black-labelled drugs





# Prevention of hERG current inhibition



- Manual patch-clamp, physiological temperature, using HEK293 hERG-expressing cells.
- Nilotinib and Crizotinib both inhibit hERG, and received a QTc warning label.
- EU-8120 removes the hERG inhibition completely when administered at a ratio of 9:1

# Conclusion Wrap-up

- Streptozotocin-induced type-1 rats exhibit QTc prolongation (Shimoni 1994, Ren 1997, etc.)
- Insulin depletion plays a role in the prolongation of QTc in the type-1 diabetic rats (Harris, 1996)
- The extent of QTc prolongation can be dialed in with insulin pumps
- Type-1 diabetic rats are more sensitive to QT-prolonging drugs (reduced repolarisation reserve)
- Maintaining a functional hERG signal contributes to preventing QTc prolongation in type-1 diabetic rats (EU-8120)
- *Not shown: In contrast, maintaining hERG function is NOT sufficient to prevent drug-induced LQT in type-2 rats: EU-8120 prevents hERG inhibition by nilotinib, but not nilotinib-induced LQT. The core difference between the two types of diabetic rats is the circulating insulin level.*

# Special thanks

- *Lawrence Helson (SignPath Pharma)*
- *George Shopp (Shopp Consulting)*
- *Walt Shaw (Avanti Polar Lipids)*
- *Marie-Claude Benoît IPST*
- *Sabrina Baillargeon IPST*
- *Rosie Kryczka IPST*
- *Annie Bouchard IPST*

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