Preclinical Approaches to Assess Potential Small Molecule Kinase Inhibitor-Induced Cardiac Toxicity: Past, Present, and Future

Baichun Yang, MD, PhD, DABT
FDA/CDER/OND/DCRP

Opinions presented here are those of the speaker, and do not necessarily reflect the official views of the Food and Drug Administration

What was realized ~10 years ago

- Left ventricular functional declines in TKI-treated cancer patients were unexpected.
- TKI-induced left ventricular dysfunction was not well predicted by standard preclinical studies
  - Safety pharmacology studies - Acute
  - Non-clinical Evaluation of QT Interval
  - Toxicity Studies – No evaluation for cardiac function
- Gaps and proposed preclinical approaches (5-10 years ago)
  - A comprehensive KI mechanism of action determination
  - Appropriate cardiac functional evaluation

Documented Achievements during Last 5 years

- The potential for sunitinib and sorafenib to cause cardiac toxicity in humans was demonstrated by Henderson KM et al. using a Langendorff perfusion system (J Pharmacol Toxicol Methods 2013; 68: 150-159)

- Jacob F et al. demonstrated the feasibility to study TKI-mediated force effects in a three-dimensional, force-generating engineered heart tissue (EHT) model and identified decline in contractile force in 7 of 9 TKIs (PLoS ONE 2016; 11: e0145937).

Documented Achievements during Last 5 years

- hiPSC-CMs for preclinical cardiac functional evaluation and KI cardiotoxic MOA studies, examples:
  - A multi-parameter in vitro screen in hiPSC-CMs identified ponatinib-induced structural and functional cardiac toxicity, and accurately predicted the cardiac toxicity potential of ponatinib (Talbert DR et al., Toxicol Sci 2015; 143: 147-155)
  - Sharma A et al. screened 21 marketed TKIs for toxicities in hiPSC-CMs, generated cardiac safety indices, and demonstrated that TKIs with low cardiac safety indices exhibit cardiotoxicity in patients (Sci Transl Med 2017; 9: eaaf2584)
  - Data generated by Yang X et al. showed a positive predictive power of 80% and negative predictive power of 50% in predicting human KI cardiotoxicity as defined by product labeling (SOT meeting, March 2017)

Documented Achievements during Last 5 years

- More recently approved KIs have been publicly documented with various KI-induced cardiotoxicity in preclinical studies (submitted for regulatory review). Predictive examples include:
  - Trametinib (2013) decreased heart rate, heart weights, and left ventricular functional parameters in mice at the end of a 21-day oral dosing study.
  - Cobimetinib (2015) increased findings of cardiomyopathy compared to findings in control animals in a 4-week rat toxicology study.
  - Osimertinib (2015) decrease in LV dP/dTmax in dogs and guinea pigs.

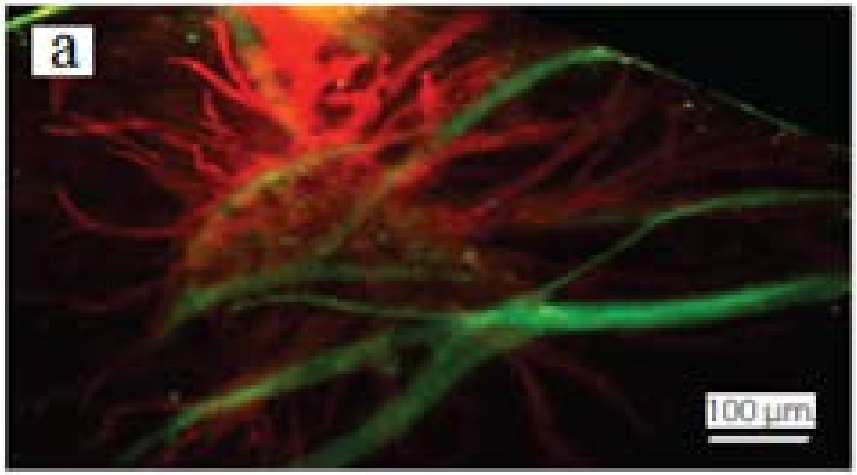
Current Status

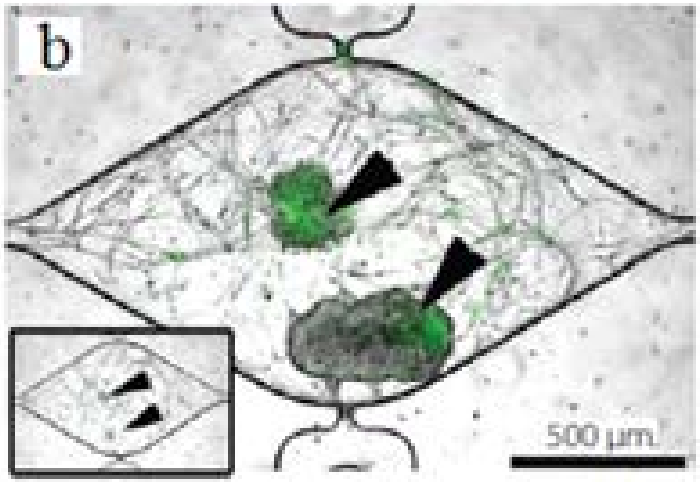
- Early identification and assessment of KI-induced cardiotoxicity in the preclinical setting are now possible.
- Given KI MOA on affecting diverse cellular processes common to both normal and tumor cells, cardiotoxicity with KIs appears difficult to avoid.
- Patient survival periods are significantly prolonged, and cardiovascular toxicities (*e.g.* heart failure) become less acceptable.
- **Need drugs with less or no unwanted adverse effects**

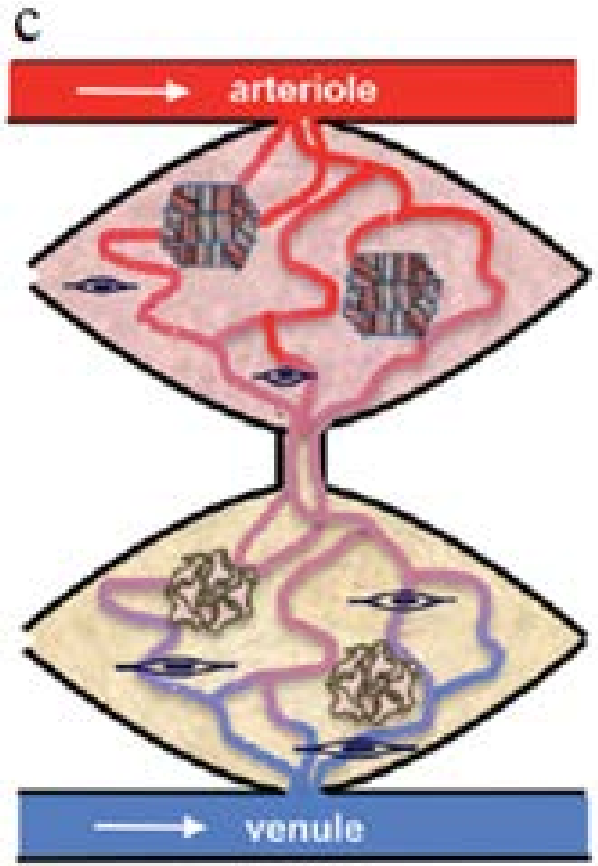
Future Preclinical Approaches to Lower Cardiovascular Risk

- Target - Identify different genomics/proteomes between normal and tumor tissues and obtain cancer specific gene-protein expression
- Concentration - Separate drug concentrations for anti-tumor activity from cardiac toxicity
  - Animal models of disease: oncology is the therapeutic area where are most frequently used for nonclinical safety assessment for decades (useful in candidate selection)
  - 3D microfluidic organ systems (“tissue chips”): an integrated in vitro model of perfused tumor and cardiac tissues (Steven C George’s group) (useful in screen)

Moya M, Tran D, and George SC. An integrated in vitro model of perfused tumor and cardiac tissues. Stem Cell Research & Therapy 2013; 4: S15







Conclusion

- Past - TKI-induced cardiac toxicity was not well predicted in preclinical tests
- Current - KI-induced cardiac toxicity is detectable with various preclinical tests
- Future – Better KIs via identifying cancer-only targets and/or separating doses for efficacy from cardiac toxicity

Minimizing and predicting potential KI-induced cardiotoxicity are still important regulatory challenges, and better preclinical approaches may help to achieve these goals.

Acknowledgement

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Thomas Papoian

Xi Yang

Backup Slides

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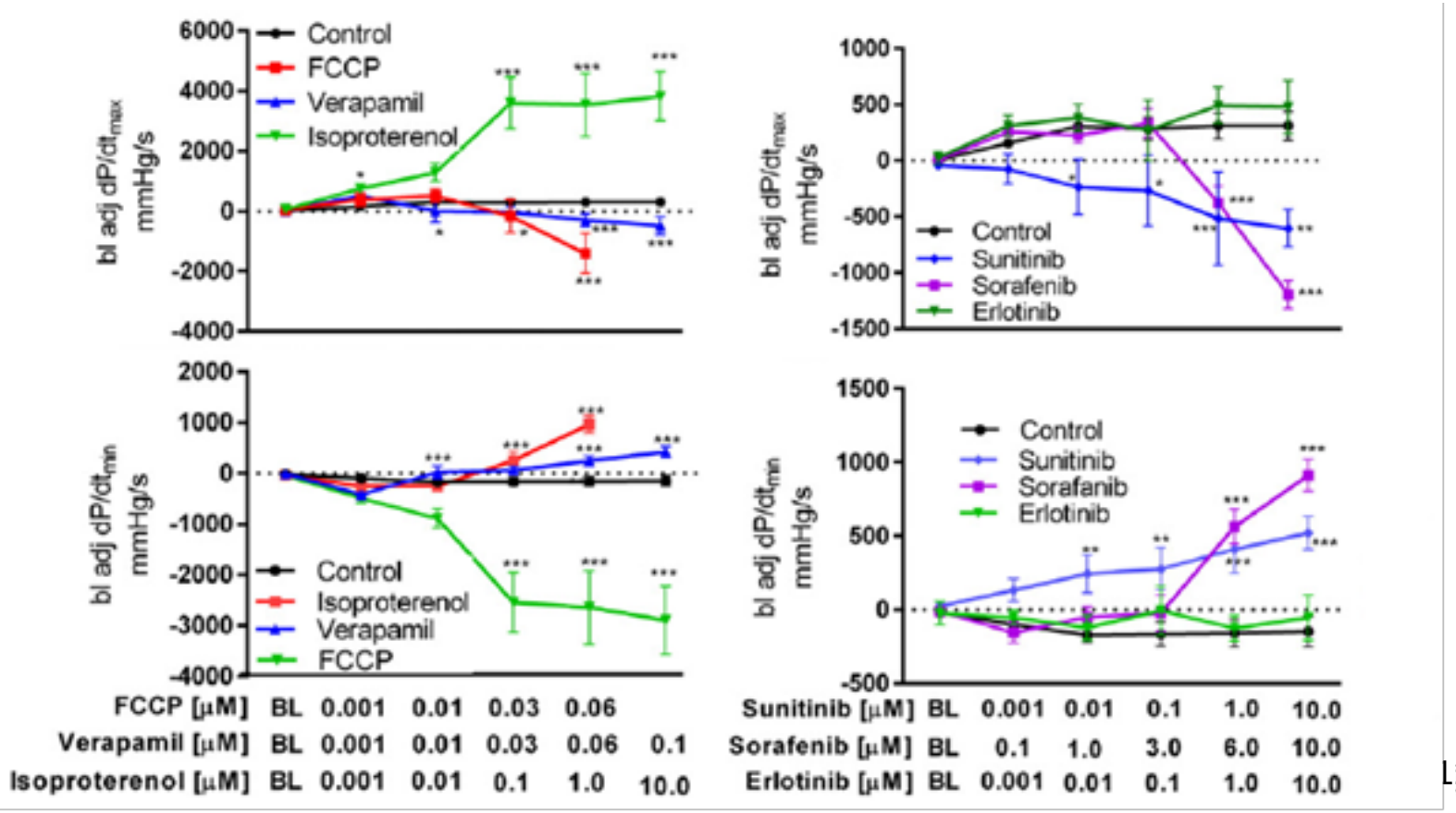
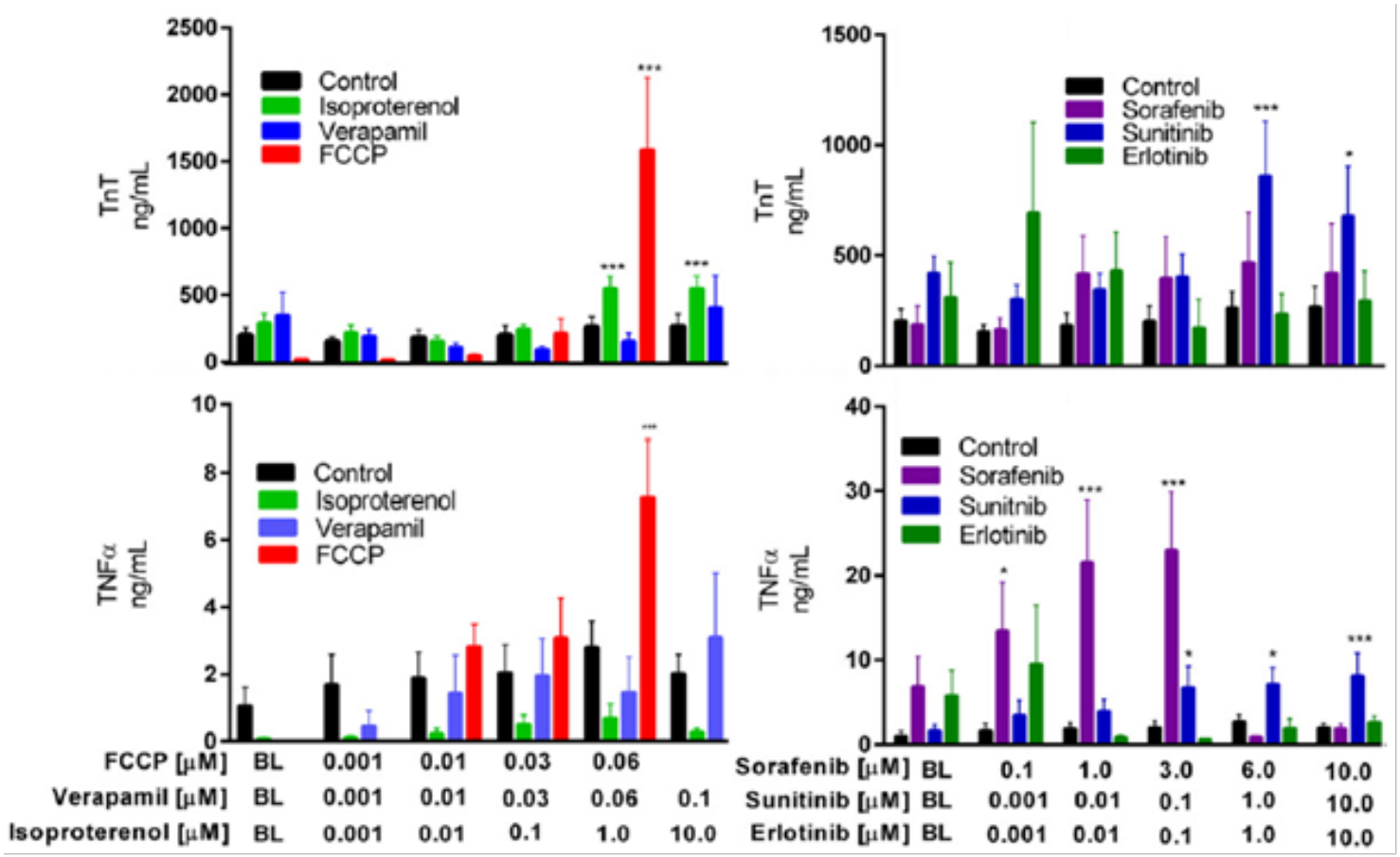


Henderson KM et al. 2013. TnT and TNFα in effluent collected at the end of each 20 min concentration period from isolated hearts perfused with tested articles (n=3-7)



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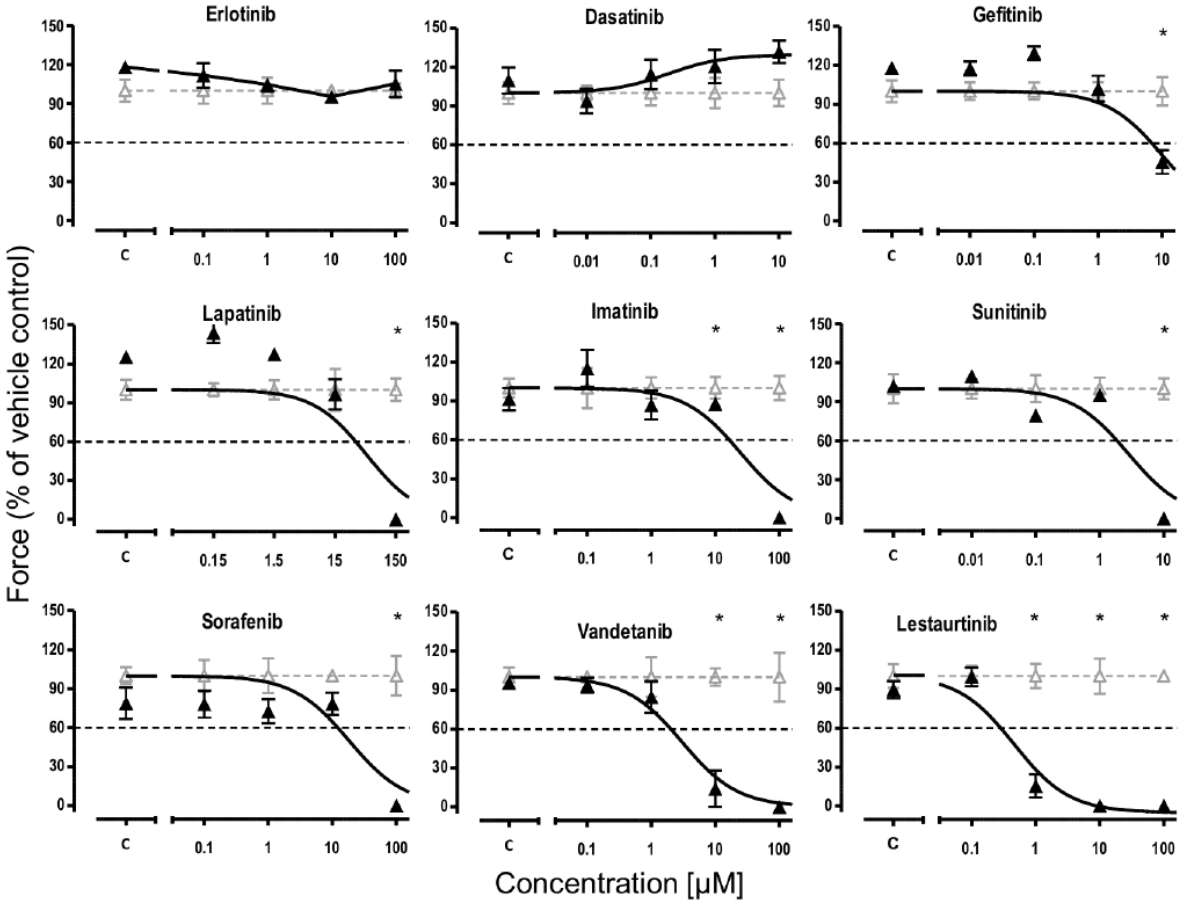

Jacob F et al.: Effect of TKI on EHT contractility: Toxic threshold concentration (40% reduction in EHT contractile force) and safety margin (PLoS ONE 2016; 11: e0145937

	Therapeutic plasma concentration (TPC, µM)	Toxic threshold concentration (TTC, µM)	Safety margin (TTC/TPC)
Erlotinib	2.5 µM [1]	n/a	n/a
Dasatinib	0.04 µM [2]	n/a	n/a
Gefitinib	0.116 µM [3]	6.29 µM	54
Lapatinib	1.1 µM [5]	31.38 µM	29
Sunitinib	0.2 µM [4]	18.99 µM	95
Imatinib	2.02 µM [6]	1.88 µM	0.9
Sorafenib	6.5 µM [9]	12.71 µM	2.0
Vandetanib	2.1 µM [7]	2.08 µM	1
Lestaurtinib	7.7 µM [8]	0.28 µM	0.04

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Drug	Cessation of beating (μM)	Effective concentration (μM)	Amplitude of effect	LD_{50} (μM)	C_{max} (μM)	Cardiac safety index	Clinically reported cardiotoxicity
Vemurafenib	33	11.00	0.34	32.10	126.04	0.003	QT
Sorafenib	3.7	2.51	1.03	3.40	8.43	0.004	QT, LV, HF, MI, Hy
Doxorubicin	3.7	1.20	0.60	0.78	2.93	0.010	****HF, LV**
Regorafenib	11	3.70	0.84	7.10	8.08	0.010	#MI, Hy
Vandetanib	33	5.68	2.47	20.60	4.26	0.041	****QT, TdP, SCD, HF, Hy**
Crizotinib	11	1.91	0.59	8.60	1.24	0.063	QT, Brady
Nilotinib	100	8.31	2.65	29.00	4.27	0.104	****QT, LV, Vas**
Imatinib	100	33.00	1.59	78.20	5.11	0.126	LV (rare)
Lapatinib	33	11.00	0.40	100.76	2.30	0.209	#LV, QT
Sunitinib	3.7	0.81	1.33	12.70	0.18	0.218	#HF, LV, MI, QT, Hy
Bosutinib	33	4.73	1.92	12.39	0.51	0.315	PE
Gefitinib	33	3.11	1.24	26.30	0.45	0.409	None
Afatinib	3.7	1.65	1.11	12.30	0.10	0.444	None
Dabrafenib	100	36.75	0.71	100.68	4.16	0.459	LV
Ponatinib	3.7	3.70	0.54	4.30	0.14	0.483	****Vas, HF, LV, Hy**
Ibrutinib	33	10.01	1.54	11.90	0.37	0.507	Afib
Dasatinib	3.7	1.20	0.31	42.00	0.21	0.524	QT, PE, Hy
Erlotinib	N/A	63.38	0.51	87.60	3.11	0.653	MI (rare)
Pazopanib	N/A	73.86	1.19	N/A	103.08	0.671	#QT, LV (rare)
Cabozantinib	N/A	91.14	1.37	N/A	4.43	0.769	#None
Trametinib	100	33.00	2.37	66.80	0.02	1.000	LV
Axitinib	N/A	71.79	0.44	N/A	0.07	1.000	HF (rare) Hy
DMSO	N/A	100.00	0.58	N/A	N/A	1.000	None

Yang X et al. Effect of KIs on calcium transient signal in hiPSC-CM (SOT meeting, March 2017)