

Cardiac Safety Evaluation Service

NeXST

Next Xight Screening Test

NEXEL's Cardiac Safety is the New Paradigm



Our story

Various new medicines are being developed thanks to the development of science and medicine. As methods for confirming the efficacy and safety of new drug candidates have also developed, safety evaluation methods using iPSC-derived cells are drawing attention.

Nexel is a bio-specialized company that recognizes this market trend, commercializes "Korea's first" induced pluripotent stem cell (iPSC)-derived cell products, and provides hiPSC-Cardiomyocyte based cardiac safety screening service.



Make a better place

Nexel Co., Ltd. aims to lead innovative research using high-quality iPSC-induced cell products and contribute to the enhancement of human health and welfare by discovering new drug candidates to treat various diseases.

Contribute to a better life through trusted research

Nexel would like to help improve the research environment of researchers by producing better quality products based on our leading-edge technologies.

We also aim to ultimately improve the patients' quality of life by investing resources in the discovery of new protein and peptide drug candidates that target various acute chronic diseases without approved treatments yet.

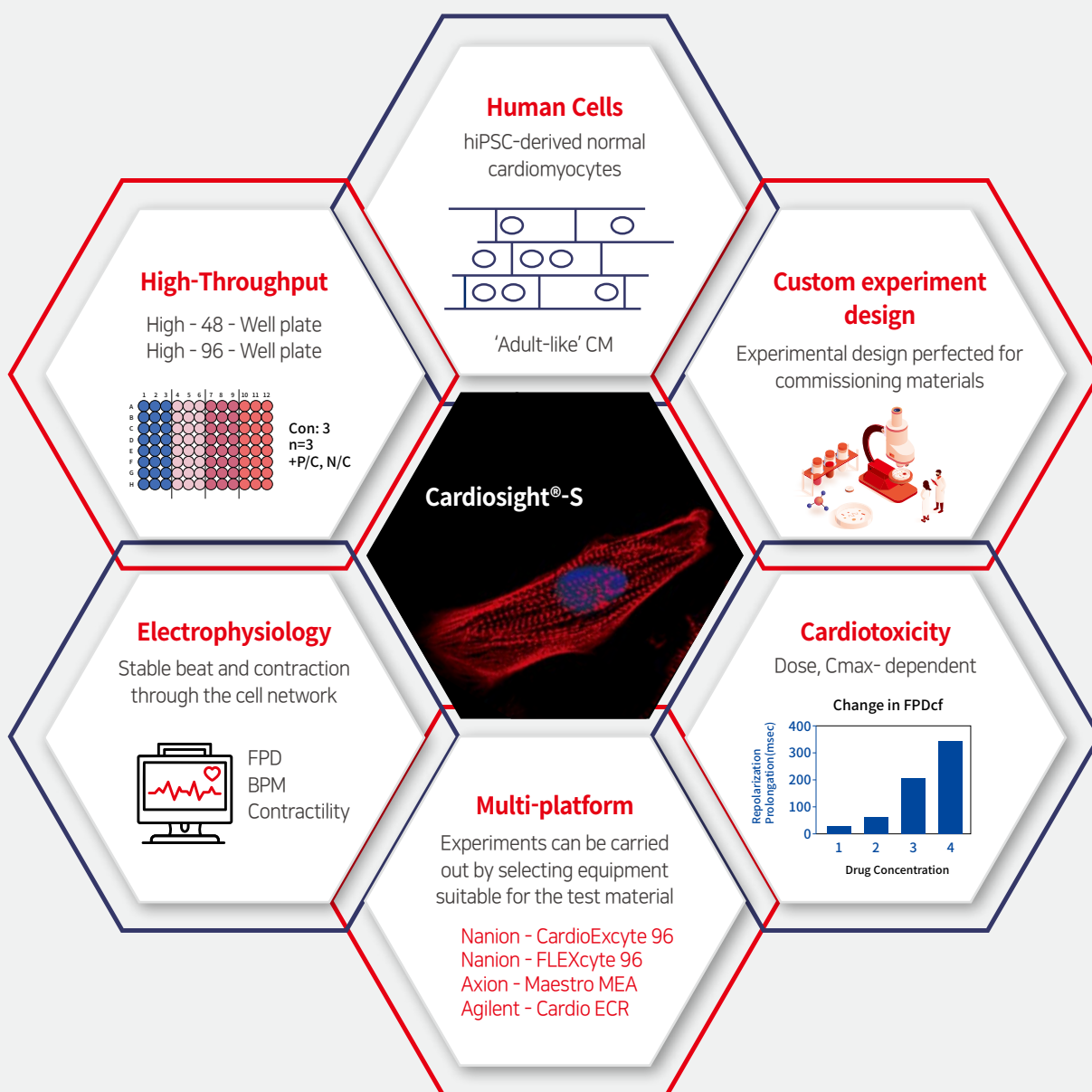


NeXST service

NeXST (Next Xight Screening Test)- (Cardiac Safety Evaluation Service)

NeXST is Nexel's pharmacology test service for cardiac safety that predicts and evaluates the risk and harmfulness of the human heart using hiPSC-CM to enable more efficient development of new drugs.

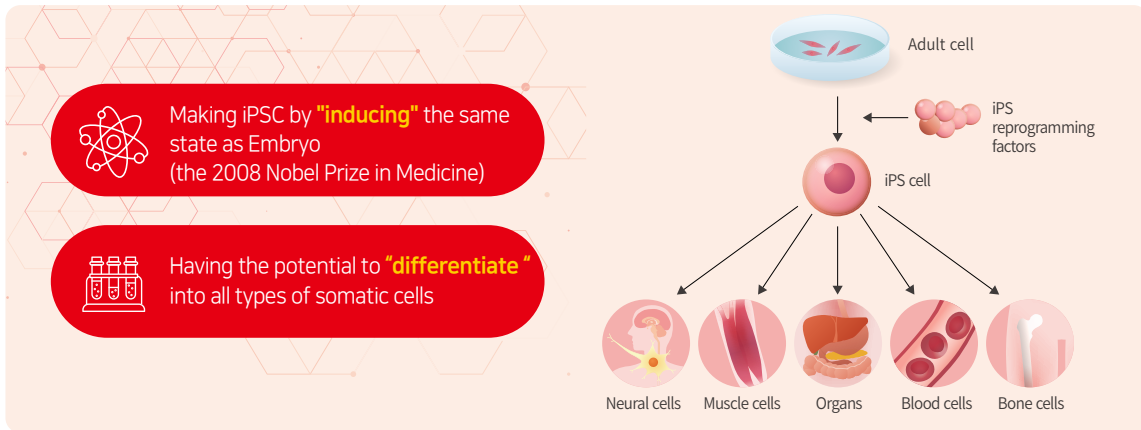
Nexel Co., Ltd. is the only company in Korea that is participating in the revision of ICH guidelines as a member of HESI CIPA Working Group. Our cardiac safety pharmacology test platform has verified the exact derivation of results using various standard reagents, and offers services using Cardiosight®-S, a self-produced iPSC-derived cardiomyocyte, to suggest flexible experimental design and reasonable costs.



iPSC : induced Pluripotent Stem Cells

Induced Pluripotent Stem Cells?





Induced pluripotent stem (iPS) cells are a type of pluripotent stem cell-derived from adult somatic cells. They have been reprogrammed by inducing genes and factors to be pluripotent. iPS cells are similar to embryonic stem (ES) cells in many aspects.



Making iPSC by **"inducing"** the same state as Embryo (the 2008 Nobel Prize in Medicine)

Having the potential to **"differentiate"** into all types of somatic cells

A new paradigm for toxicity assessment

	Accuracy of the results	Ethical issues	Variation between the batches	Ease of cultivation	Mass production	Genetic modification	Establishing a test method
 animal model	Inaccurate (difference between species)	Yes	Yes	N/a (high breeding cost)	Labor and cost-intensive	No	Yes
 Human Primary Cells	Accurate	Yes	Yes	Yes	Impossible	No	No
 Immortalized Cell lines	Inaccurate (abnormal cells)	No	No	Easy	Easy	Yes (abnormal cells)	No
 hiPSC-derived cells	Accurate	No	No	Easy	Easy	No	Revision in progress by ICH



NEXEL's iPSC-derived cell products

- ✓ New toxicity test model
- ✓ Overcoming limitations
- ✓ **Functional human cells!**
- ✓ Reproducibility UP!



Cardiosight®-S
cardiomyocytes



Neurosight®-S
neurons



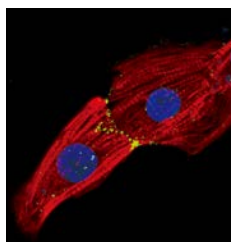
Hepatosight®-S
hepatocytes

Cardiosight®-S

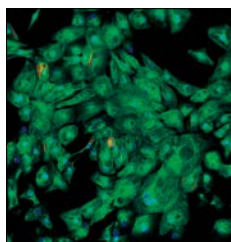
Nexel utilizes its own optimized iPSC-induced differentiation technology to provide Cardiosight®-S, a high-quality cardiomyocyte product with functionality similar to that of real human cells.

- High Sensitivity**
 - Drug responsiveness suitable for myocardial toxicity/safety assessment
 - Expression for the ion channel of human cardiomyocyte
- Consistent Quality**
 - Quality control through ISO9001 certification and molecular /electrophysical experiments
 - Used in research to revise ICH guidelines for cardiac safety assessment
- Ready To Use**
 - Possible to test electrophysiology after 7 days of thawing
 - Always in stock, and possible to order in bulks
- Technical Support**
 - Invigorated on-site technical support
 - Direct and prompt response from the research institute in charge of technical support
- Field of Use**
 - Electrophysiology experiment
 - Various cell application experiments
 - Toxicity and safety test

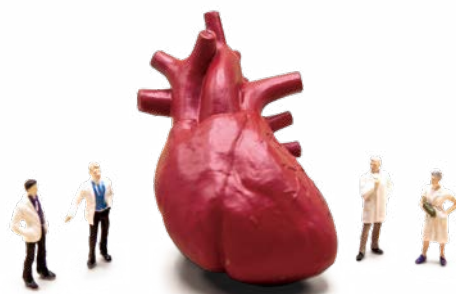
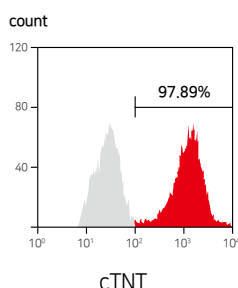
High purity cardiomyocytes



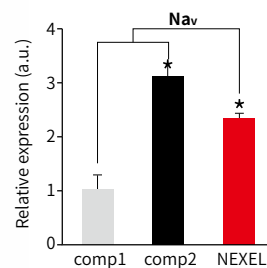
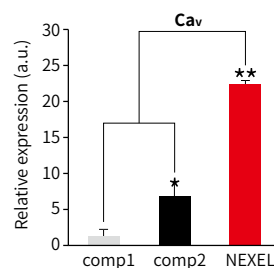
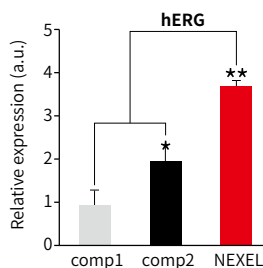
cTNT connexin43 DAPI



MLC2A MLC2V DAPI



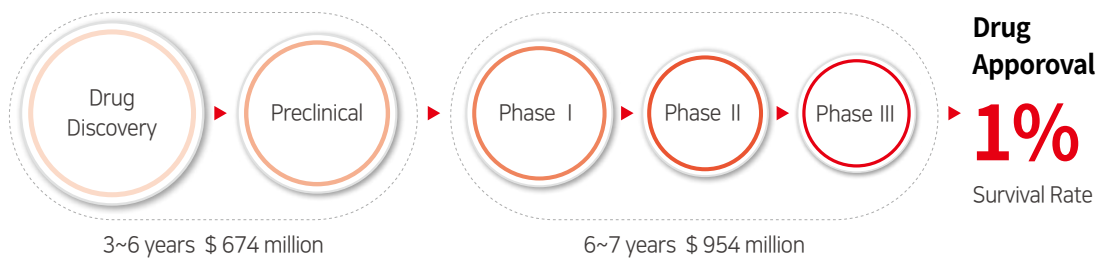
Gene expression related to cardiomyocyte ion channels



By the post-hoc Tukey test, **: p<0.01 * : p<0.05

Importance of Cardiotoxicity Assessment

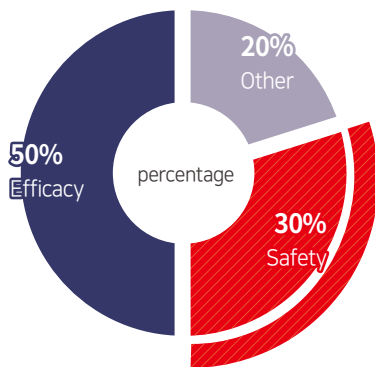
\$1 to 2 billion and a period of **9 to 13 years** are needed for the new drug to successfully enter the market.



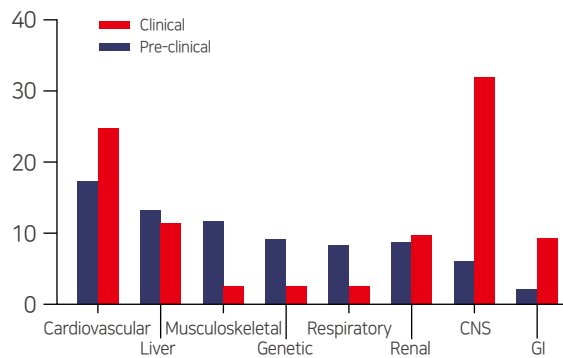
Adapted from Scannell et al. 2012

More than 50% of the eliminated new drug candidates are excluded from candidate materials due to insignificant effects and **more than 30%** due to safety issues.

A : Drug development discontinuation Reason



B : Drug safety failures by organ system



A: Safety Pharmacology Society industry survey, 2000-2016 (Valentin & Redfern 2017). B: AstraZeneca data, 2005-2010 (Cook et al. 2014)

Cardiotoxicity is still a major cause of side effects and failure to meet the safety standards of new drugs.



Cardiotoxicity is the leading cause for drug attrition (Car, 2006)



45% of all drug withdrawals are related to **cardiovascular** issues (Stevens and Baker, 2009)

ICH S7B

(The Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarization(Qt Interval Prolongation) by Human Pharmaceuticals)

| Safety Pharmacology Studies for Human Pharmaceuticals

A test to evaluate the efficacy and the risk of a drug that may appear in people with limited organ function, irrelevant to the originally intended therapeutic effect when developing medicine and medical supplies

| ICH Guideline S7B

- ① Identifying the possibility of delay in ventricular repolarization of test materials and metabolites
- ② Identifying the correlation between the concentration of the test substance and metabolite and the degree of delay in ventricular repolarization



hERG channel blockers cause the extension of APD in ventricular muscle cells and drug-induced long QT syndrome in the heart can lead to blackouts and sudden death.



Drug-induced long QT syndrome is a result of repolarization abnormalities, which can lead to rapid and disorderly poly-ventricular tachycardia (Torsade de points, TdP), causing fatalities resulting in death.



Up to 34% of drug withdrawal from 1990 to 2006 is taken by previously approved drugs due to their prolonged QT intervals or side effects that cause cardiac arrhythmia, and their use was strictly restricted.

Advantages High sensitivity

- ① Effective in preventing them from dangerous hERG channel blockers' being sold on the market.
- ② Very sensitive, so even small changes in QT intervals can be detected.

Disadvantages Not specific

- ① Taking a considerable amount of time and money.
- ② The accuracy of arrhythmia risk declines.



CIPA's ICH S7B Amendment

ICH S7B amendment of CIPA (Comprehensive *in vitro* Proarrhythmia Assay)

- Unlike the existing focus on cardiac repolarization delay (QT interval extension), evaluation was conducted focusing on arrhythmia.
- Provides a more balanced assessment of the risk of the patient's heart

1

modified from Hoekstra et al., 2012

Drug Effects on Multiple Human Cardiac Currents

2

$$I_{stim} = C \frac{dV_m}{dt} + I_m$$

In Silico Reconstruction Human Ventricular Cellular Electrophysiology

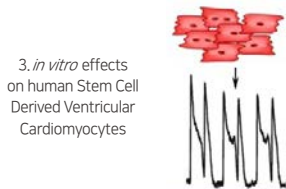
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McEwen Cntr for Regen Med., Toronto

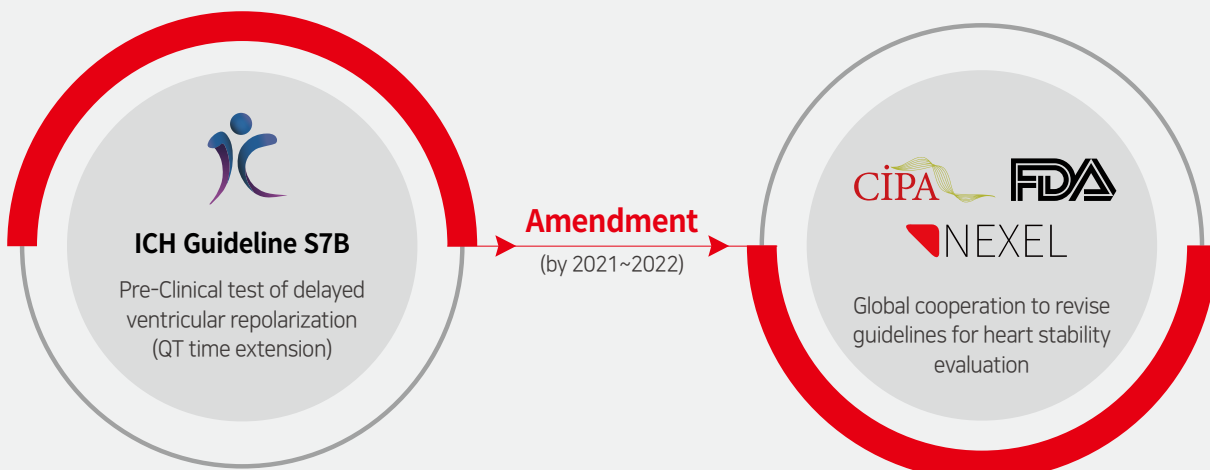
VSD
MEA

In Vitro Effects Human Stem-Cell Derived Ventricular Myocytes

Analysis using human induced pluripotent stem cell-derived cardiomyocytes (3rd CiPA pillar)

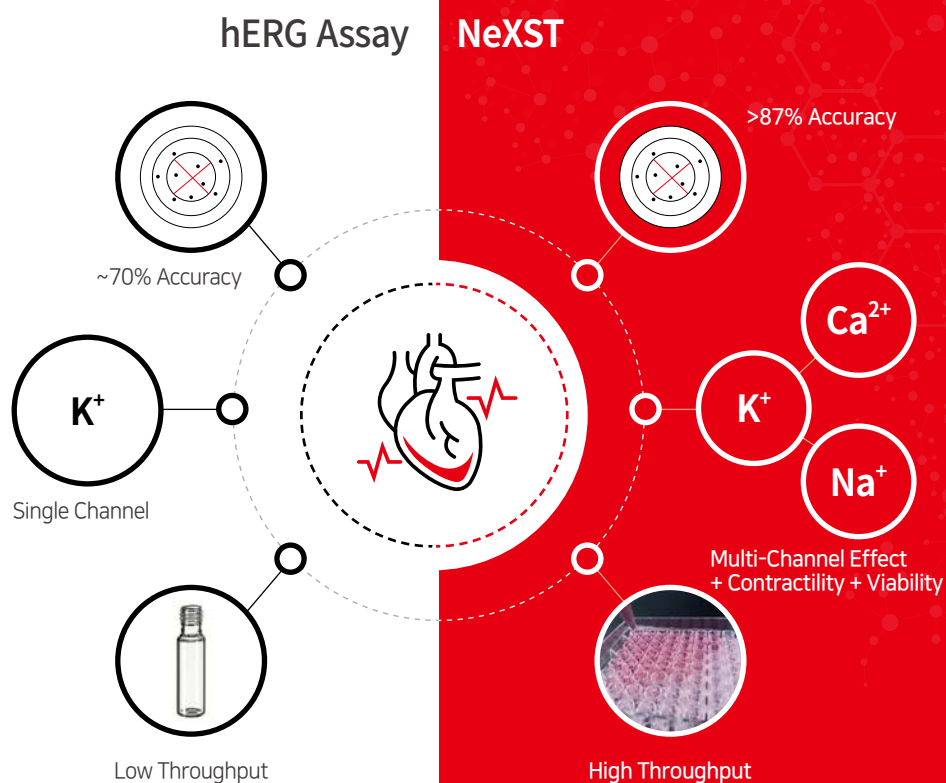


- The third pipeline of CiPA uses iPSC-CM that is similar to the human heart and can serve as an experimental model. It is designed to be verified via various analysis methods.
- hiPSC-CM performs voluntary AP blowing and beating and is easy to check the electrophysiological response of cardiomyocytes to drugs.



NeXST – Cardiac Safety Evaluation Service

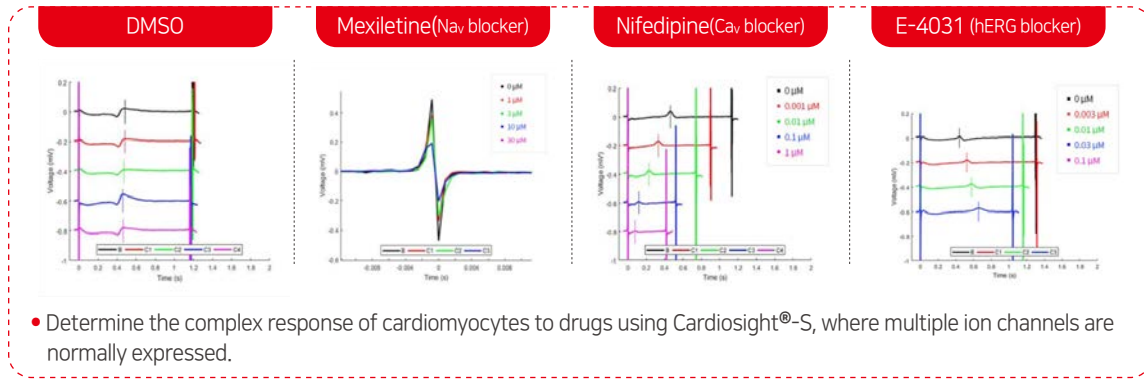
Nexel's own Cardiac Safety Evaluation Service in compliance with the CIPA ICH S7B amendment



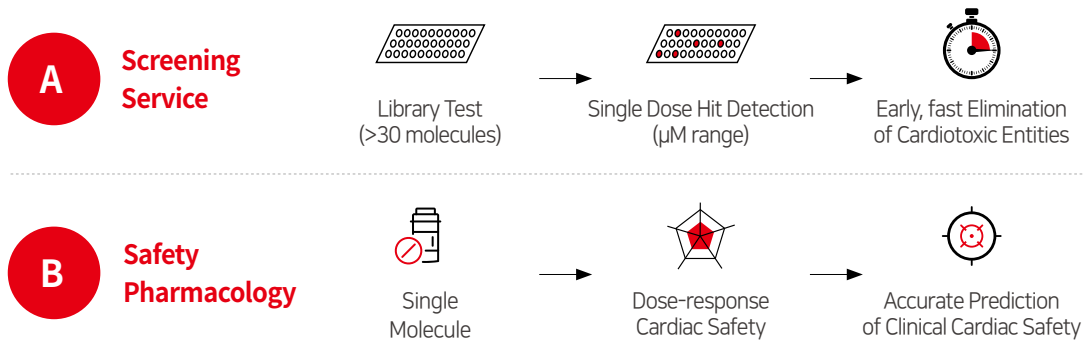
	hERG Assay	NEXEL Cardiac Safety
Target	Single Channel Effect	Multi-Channel Effect + Contractility + Viability
Result	hERG Inhibition Curve	QT(FPD) Prolongation + Proarrhythmic Risk
Accuracy	~70%	>87% (Blinova et al.) 100% (Clyde)
Toxicology	Acute Effect Only	Chronic Effect (optional)
Specificity	Low (False Positive, e.g. Verapamil)	High
Throughput	Low-1 drug per day (n=5)	High-96-Well plate

NeXST – Cardiac Safety Evaluation Service

NEXEL provides its Cardiac Safety Evaluation Service using its own **Cardiosight®-S**

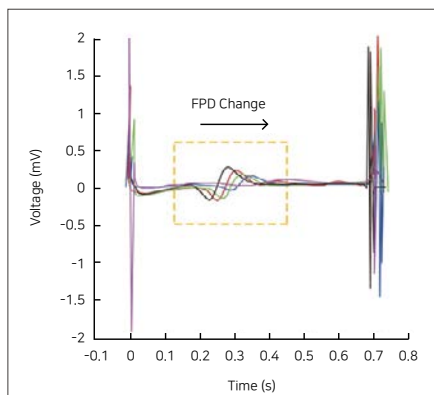
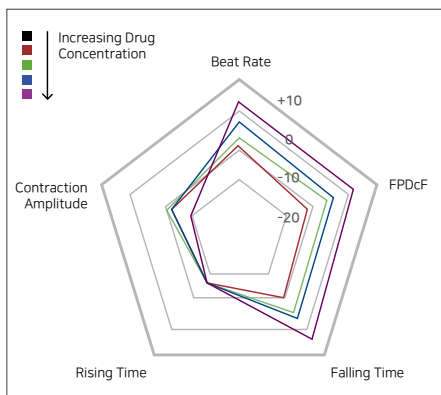


NEXEL is your **Specialist** in Cardiac Safety




• Quickly and accurately checks the safety of drug candidates *in vitro* to eliminate risk.

Example results (relative changes to vehicle)



NeXST allows a thorough analysis of not only TdP arrhythmia but also beat rate, and contraction amplitude that can **improve the understanding of drugs**



Multi-Platform

	Facilities			
	Axion Maestro MEA	Nanion CardioExcyte 96	Nanion FLEXcyte 96	Agilent Cardio ECR
Toxicity Service				
Field Potential Duration	0	0		0
Pulsewidth, Rise & Fall Time		0	0	0
Contractility		Δ (Impedance)	0	Δ (Impedance)
Beat Rate	0	0	0	0
Long-term Assessment	0	0		0
Pacing		0		0

※ You can select and proceed with the most suitable testing equipment for the requested new drug candidate.



Cardio ECR






Maestro MEA






CardioExcyte 96



FLEXcyte 96

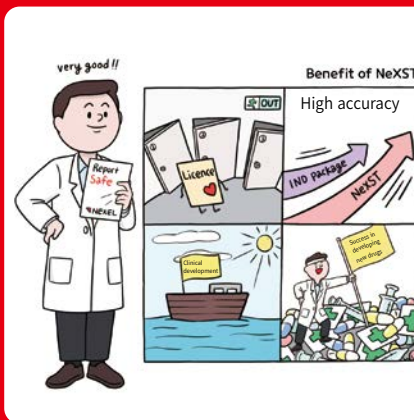
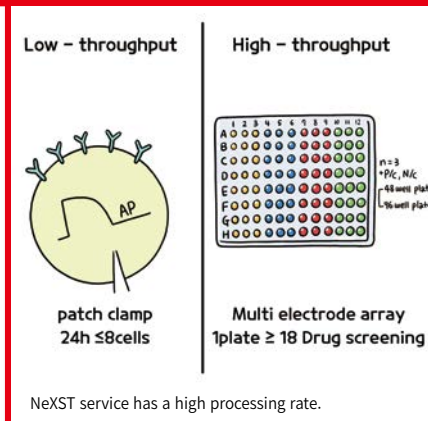
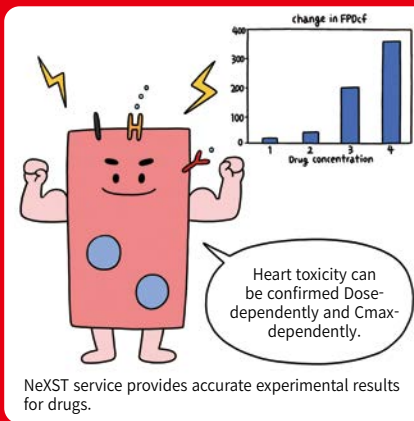
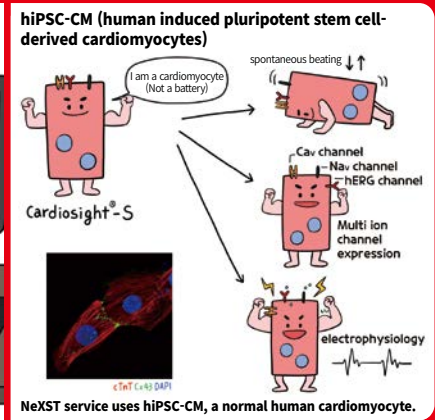


The Success Story

of the Vaccine Drug Researcher's

New Drug Development

Illustration : Neunji
Written by : Doctor Kim



NEXEL, Marcus Building 8F, 55
Magokdong-ro, Gangseo-gu, Seoul,
Republic of Korea

Tel : 02-2088-8886
E-mail : sales@nexel.co.kr
<https://www.nexel.co.kr>