Research and Development at JT's Pharmaceutical Business

July 4, 2017
Shigenori Ohkawa, Ph.D.
Head of Central Pharmaceutical Research Institute

ひとの
ときを、
想う。

FORWARD-LOOKING STATEMENTS

This presentation contains forward-looking statements. These statements appear in a number of places in this presentation and include statements regarding the intent, belief, or current and future expectations of our management with respect to our business, financial condition and results of operations. In some cases, you can identify forward-looking statements by terms such as "may", "will", "should", "would","expect", "intend", "project", "plan", "aim", "seek", "target", "anticipate", "believe", "estimate", "predict","potential" or the negative of these terms or other similar terminology. These statements are not guarantees of future performance and are subject to various risks and uncertainties. Actual results, performance or achievements, or those of the industries in which we operate, may differ materially from any future results, performance or achievements expressed or implied by these forward-looking statements. In addition, these forward-looking statements are necessarily dependent upon assumptions, estimates and data that may be incorrect or imprecise and involve known and unknown risks and uncertainties. Forward-looking statements regarding operating results are particularly subject to a variety of assumptions, some or all of which may not be realized.

Risks, uncertainties or other factors that could cause actual results to differ materially from those expressed in any forward-looking statement include, without limitation:
(1)decrease in demand for tobacco products in key markets;
(2)restrictions on promoting, marketing, packaging, labeling and usage of tobacco products in markets in which we operate;
(3)increases in excise, consumption or other taxes on tobacco products in markets in which we operate;
(4)litigation around the world alleging adverse health and financial effects resulting from, or relating to, tobacco products ;
(5)our ability to realize anticipated results of our acquisition or other similar investments;
(6)competition in markets in which we operate or into which we seek to expand;
(7)deterioration in economic conditions in areas that matter to us;
(8)economic, regulatory and political changes, such as nationalization, terrorism, wars and civil unrest, in countries in which we operate;
(9)fluctuations in foreign exchange rates and the costs of raw materials; and
(10) catastrophes, including natural disasters.

R&D Strategy

➢ The mission of JT's pharmaceutical business

- Development of world-class, unique R&D capabilities
- Reinforcement of the market presence through the development of innovative new drugs

➢ Basic strategy

- Drug discovery focused on patients' needs
- R&D aiming at First-In-Class drugs
- Focus on development of small molecule compounds
- Setting of R&D focus area based on Unmet Medical Needs
- Out-licensing to partners for global development
- Active open innovation

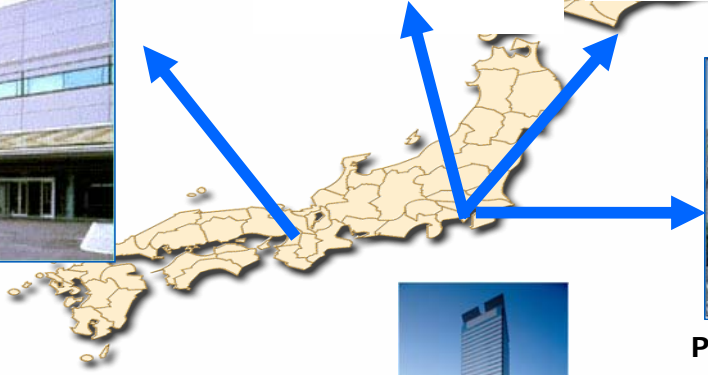
Locations of R&D facilities

Akros Pharma Inc.
(New Jersey, USA)

Toxicology Research Laboratories
(Hadano, Kanagawa)

Pharmaceutical Frontier Research Laboratories
(Yokohama, Kanagawa)

Central Pharmaceutical Research Institute
(Takatsuki, Osaka)



JT's headquarters
(Minato, Tokyo)

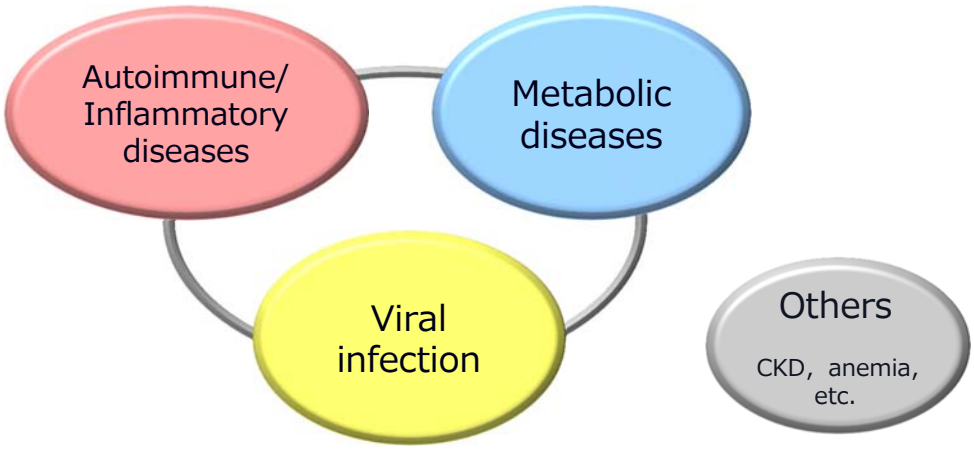
Pharmaceutical division
Torii Pharmaceutical's headquarters
(Chuo, Tokyo)

New Drugs Approved in Recent Years

Drug and indication	Year of approval
Stribild Combination Tablets **HIV infections** HIV integrase inhibitor, elvitegravir (+ cobicistat, FTC and TDF)	**Overseas (2012)/Japan (2013)** Overseas: Out-licensed to Gilead Sciences
Genvoya Combination Tablets **HIV infections** HIV integrase inhibitor, elvitegravir (+ cobicistat, FTC and TAF)	**Overseas (2015)/Japan (2016)** Overseas: Out-licensed to Gilead Sciences
Mekinist Tablets **BRAF mutation-positive melanoma** MEK inhibitor, trametinib	**Overseas (2013)/Japan (2016)** Worldwide: Out-licensed to GlaxoSmithKline (transferred to Novartis since 2015)
Riona Tablets **Hyperphosphatemia in chronic renal diseases** Ferric citrate	**Japan (2014)**

Current Focus Area

Focusing on major three therapeutic areas



- Conducting R&D on diseases having strong Unmet Medical Needs based on the future treatment paradigm (to be explained later).
- New drug targets:
  - ✓ Selecting new drug targets based on deep understanding of pathology of target diseases.
  - ✓ Setting target product profiles (TPPs) focused on differentiation from existing therapies.
  - ✓ Pursuing best practices by utilizing all available resources.

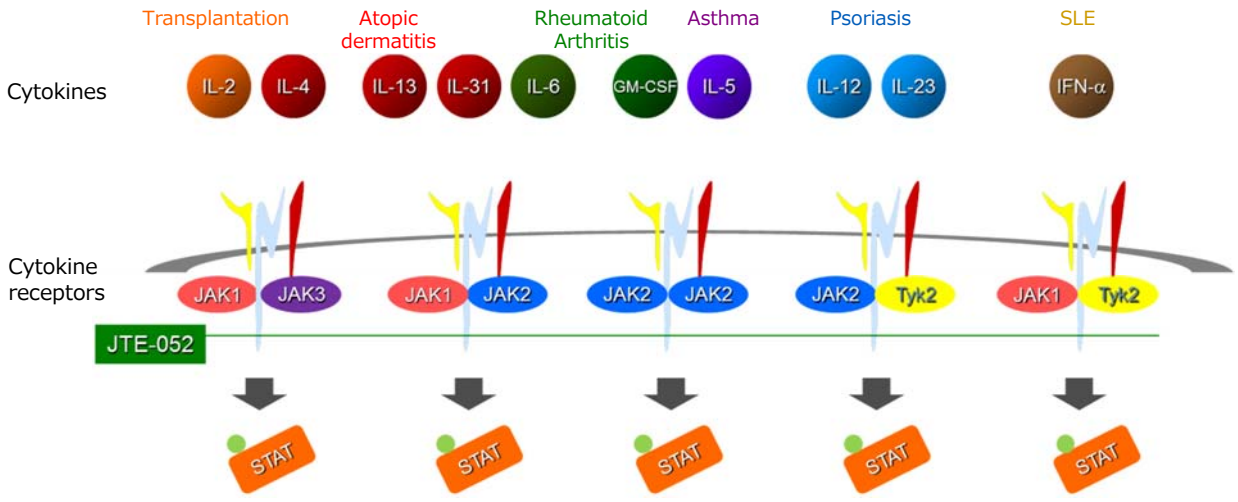
R&D Pipeline

Area	Code	Mechanism	Discovery / Preclinical	Phase 1	Phase 2	Phase 3	NDA
Autoimmune/ inflammatory diseases	JTE-052	JAK inhibitor					Japan:Ph3 Overseas:LEO
	JTE-051	ITK inhibitor				Overseas	
	JTE-451	RORγ antagonist			Overseas		
	Early programs						
Metabolic diseases	JTT-251	PDHK inhibitor			Overseas		
	Early programs						
Viral infection	JTK-351	HIV Integrase inhibitor			Japan		
	Early programs						
Others	JTT-751	Oral iron replacement				Japan	
	JTZ-951	HIF-PH inhibitor				Japan:Ph2 Overseas:Ph1	
	Early programs						

JTE-052

■ JAK inhibitor

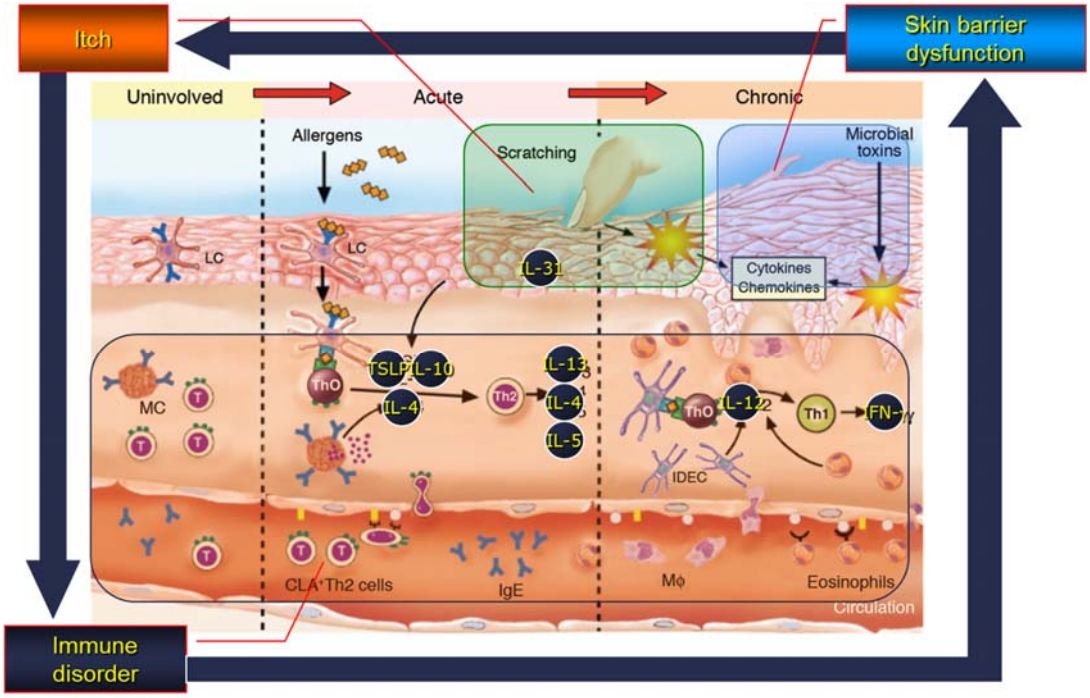
Cytokines trigger a variety of pathological conditions by activating the JAK-STAT pathway.



JTE-052 is expected to be effective as treatment for a variety of allergic and autoimmune diseases such as atopic dermatitis.

Pathological Conditions of Atopic Dermatitis

Three major factors aggravate and escalate pathological conditions by creating a vicious circle via cytokines.



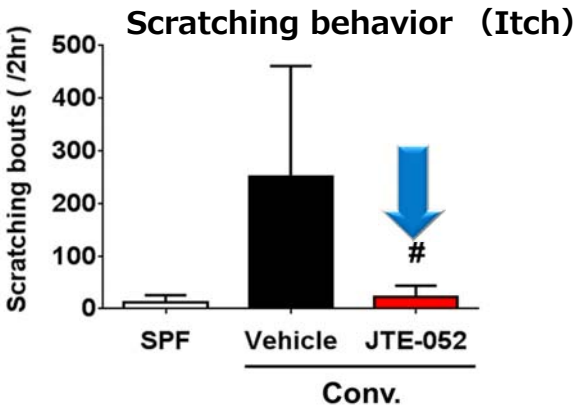
J Clin Invest. 2004 113 (5) 651-7 *revised

Clinical Expectations for JTE-052 in Treatment of Atopic Dermatitis

- JTE-052 showed significant effects on three major pathological factors in atopic dermatitis models
  - Amelioration of skin inflammation
    Clinical score ↓, Cytokine production ↓, Inflammatory cell infiltration ↓
  - Improvement of skin barrier function
    Transepidermal water loss ↓, Natural moisturizing factor ↑
    Filaggrin ↑ (cultured human keratinocytes)
  - Attenuation of scratching behavior
    Scratching bouts ↓

Vehicle **JTE-052**

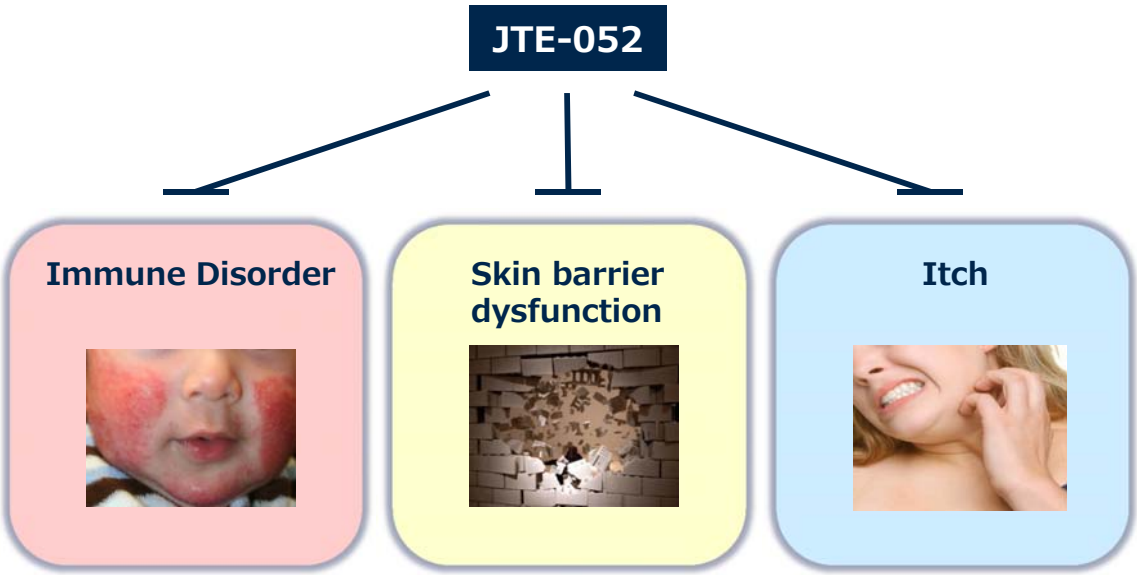
Efficacy in atopic dermatitis mouse (NC/Nga mouse)



J Allergy Clin Immunol. 2015;136:667-677
Society for Investigative Dermatology (SID) 75th Annual Meeting etc

Efficacy of JTE-052 on major three pathological factors

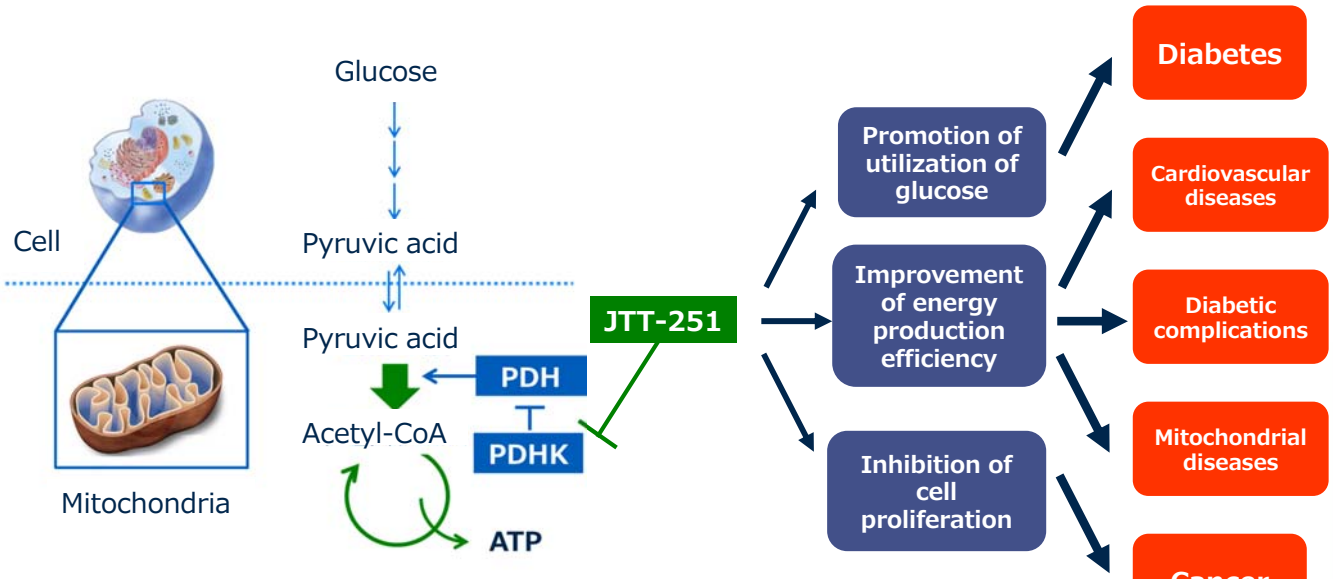
Expectations as a drug differentiated from existing treatments (Steroid/Tacrolimus)



JTT-251

■ PDHK* inhibitor

✓ PDH controls energy production from glucose in mitochondria.
✓ JTT-251 promotes the utilization of glucose by activating PDH.



*PDHK: Pyruvate Dehydrogenase Kinase

Potentials of Small Molecule Drugs

- Enable to select various drug discovery targets compared with biologics.
- Lead to discovery of entirely new mechanisms through forward pharmacology.*
- Create new value through repositioning.
- Small molecule drugs, along with cell therapy, are essential in the field of regenerative medicine.
- Enable to affect multiple targets as required for CNS drugs and so on.

- Can be administered in various dosage forms, including an oral agent.
- A patent is acquired on a compound-by-compound basis in principle.
- Can be manufactured at low cost compared with biologics.
- Ensure a high level of stability and easy quality control.
- Usually have no immunogenicity.

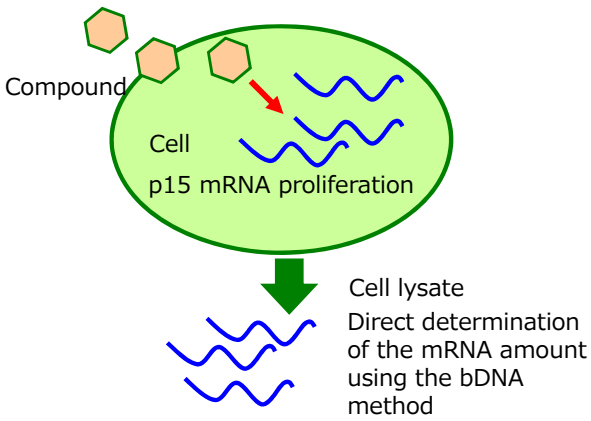
* : Approach based on the process of:
phenotypic assay → discovery of active compounds → search for drug targets

Potentials of Small Molecule Drugs – Forward Pharmacology

- Assay for a lead compound for the MEK inhibitor Trametinib

Selecting compounds that induce the activity of $p15^{INK4b}$ from the chemical library through high-throughput screening (HTS).

Branched DNA (bDNA) method



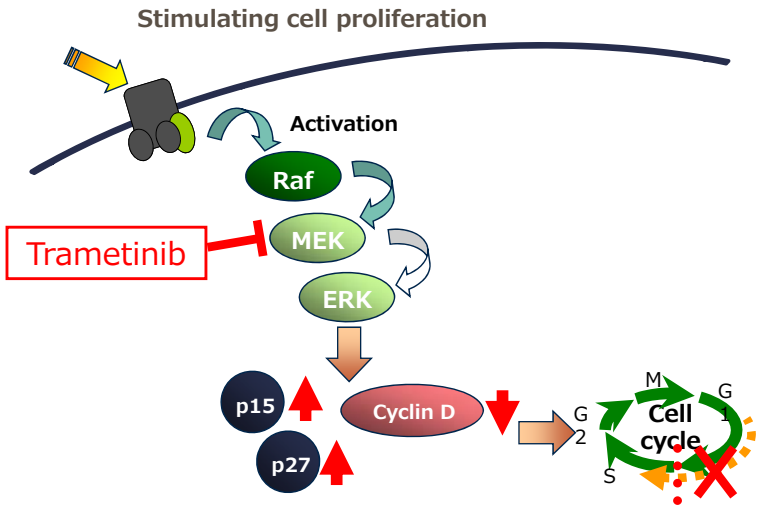
- Add a compound to normal cells.
- Dissolve cells and directly determine the amount of p15 mRNA contained in the cell lysate.
- Raise the signal sensitivity through the amplified probe technique based on the bDNA method because the amount of mRNA contained in cells is low.

Potentials of Small Molecule Drugs

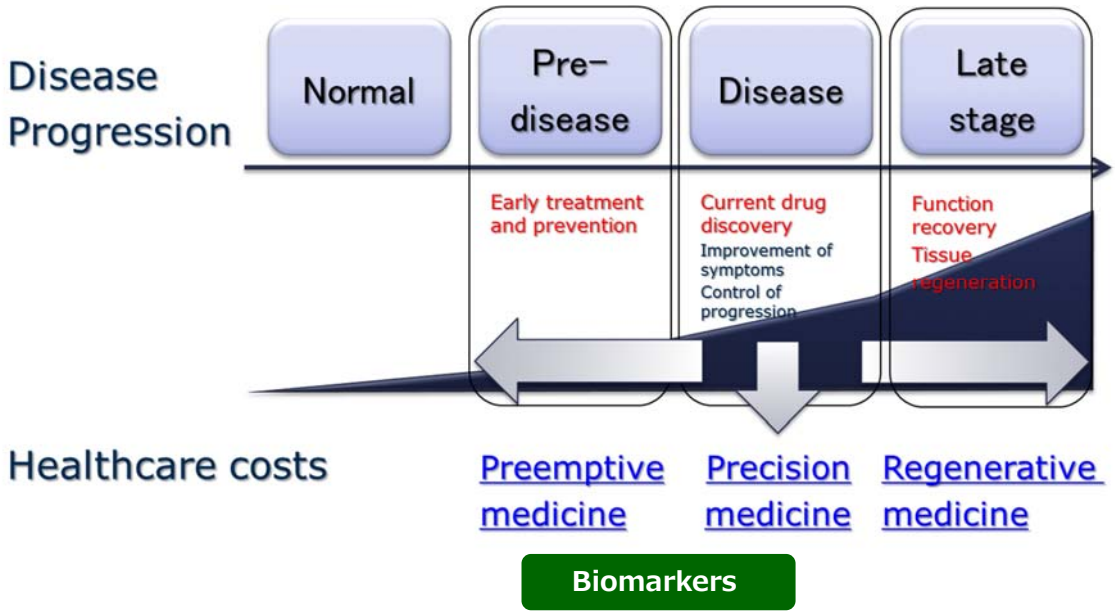
■ Search for target molecules for Trametinib through chemical biology

The target molecule for Trametinib was identified as MEK through the chemical biology method.

- ✓ Inhibit the phosphorylation of MEK by binding to unphosphorylated MEK (IC_{50} 6.7 nM).
- ✓ Inhibit the phosphorylation of ERK in the downstream by binding to phosphorylated MEK (IC_{50} 290 nM).



R&D Activities based on Future Treatment Paradigm



- ✓ Selection of drugs suited to individual patients' conditions
- ✓ Preparation for a paradigm shift in therapies toward the upstream and the downstream
- ✓ Positioning of drugs in a wide selection of therapeutic options

Open Innovation

Look outside research institutions and companies for missing pieces that cannot be internally obtained for development of First-In-Class drugs that satisfy Unmet Medical Needs.

Target discovery	Leading generation/ optimization	Preclinical
● Cause of diseases ● New drug targets etc.	● HTS ● Chemical library ● *in vitro/in vivo* assays ● Unique animal models etc.	● Biomarkers ● Repositioning etc.

- Own search for partners
- Dispatch of researchers for collaborative research
- Buildup of trust and respect

The number of joint research programs has tripled in recent years (between 2013 and 2017).

R&D Strategy

➢ The mission of JT's pharmaceutical business

- Development of world-class, unique R&D capabilities
- Reinforcement of the market presence through the development of innovative new drugs

➢ Basic strategy

- Drug discovery focused on patients' needs
- R&D aiming at First-In-Class drugs
- Focus on development of small molecule compounds
- Setting of R&D focus area based on Unmet Medical Needs
- Out-licensing to partners for global development
- Active open innovation