

ライフサイエンスデータベース統合推進事業  
統合化推進プログラム

ゲノム・疾患・医薬品のネットワークデータベース  
実施状況

京都大学化学研究所

金久 實

# KEGG NETWORK とは

NAR DB Issue 2017

KEGG: new perspectives on genomes, pathways, diseases and drugs

## From gene-disease association to network-disease association

- ヒトの疾患を、生体システムを構成する分子ネットワークのゆらぎと関連づけるという新しい概念に基づくデータベース

## From gene variants to network variants

- KEGG PATHWAY にあるレファレンスネットワークに対して、ヒト遺伝子バリエーション、ウイルスその他の病原体、様々な環境因子、医薬品などがどのようなゆらぎをもたらしているか、文献に基づく知識を集約

# 基本構想

本研究開発では、ゲノムの情報から疾患や医薬品に関する知見を得るための新しいデータベースとして、ヒトゲノムのバリエーション（多様性）を、生体システムを構成するネットワーク要素のバリエーションとして蓄積した KEGG NETWORK を開発する。KEGG MEDICUS には疾患情報、医薬品情報、ネットワーク情報が統合され、クリニカルシーケンシングデータの解釈や医薬品標的分子の探索など、ゲノム情報有効利用のための新たなレファレンスリソースとして提供する。

ゲノム情報を社会で活用するための基盤データベース

## KEGG MEDICUS

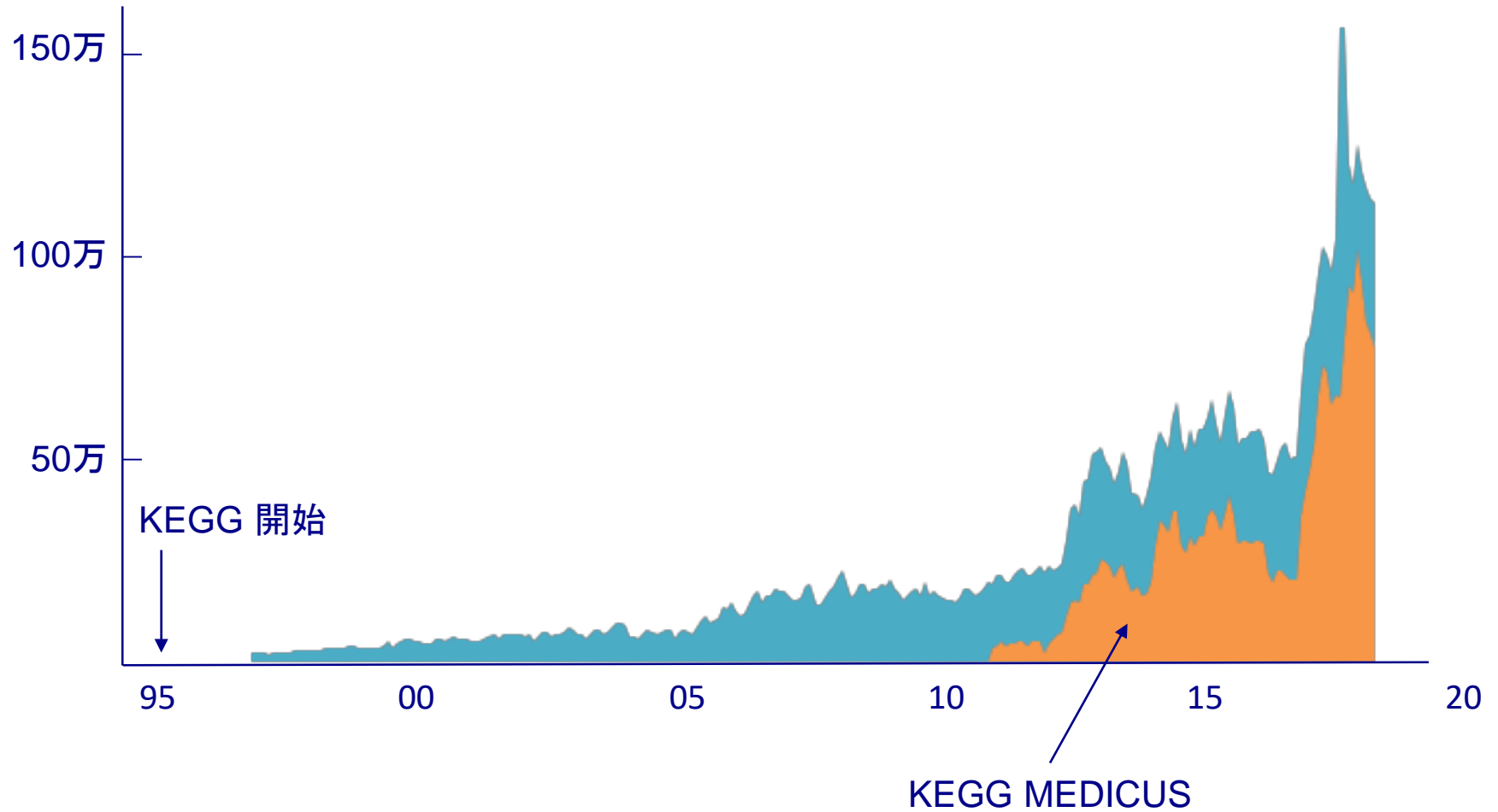
研究者  
コミュニティ



医療従事者  
一般の人々

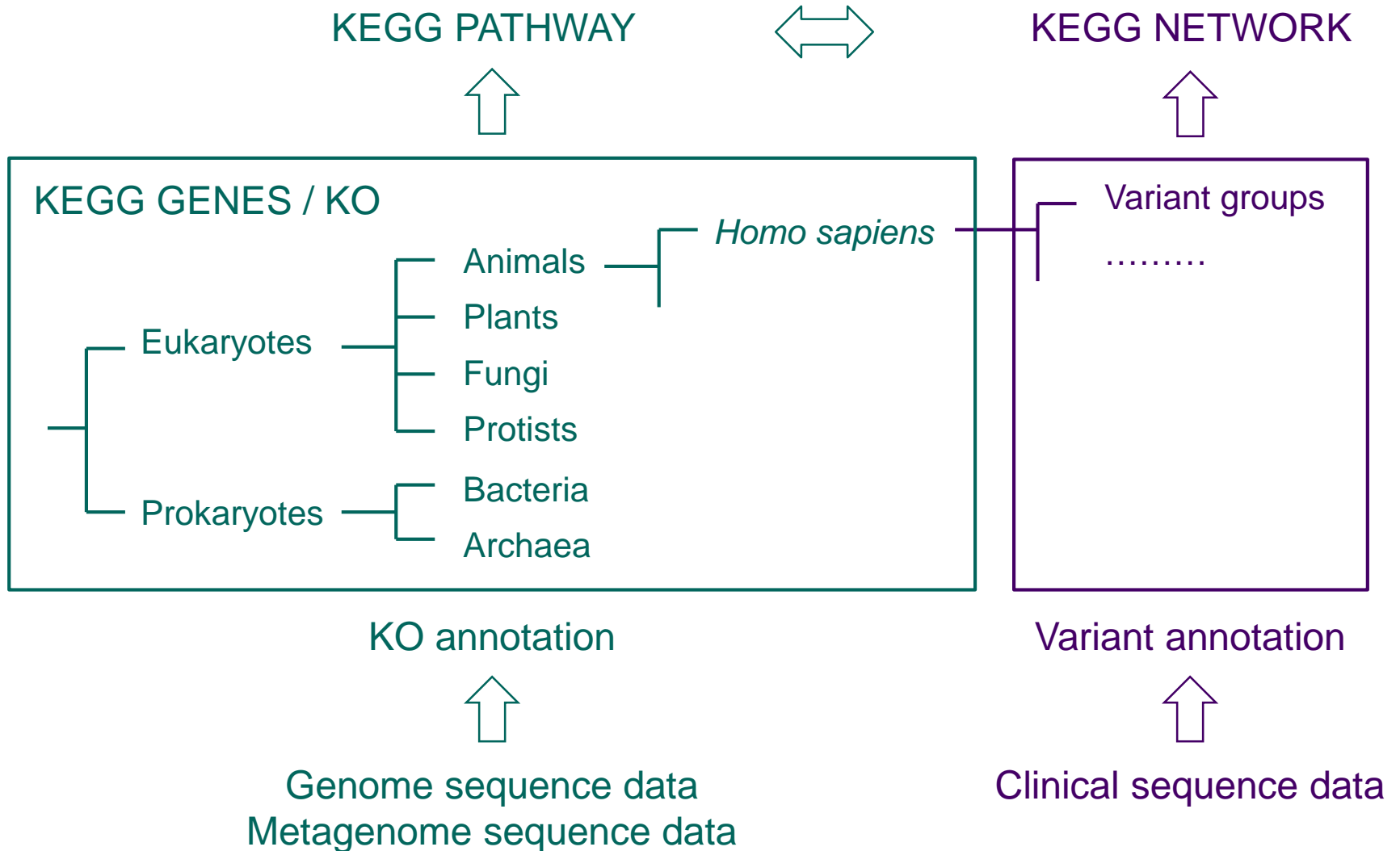
# KEGG/GenomeNet ウェブアクセス統計

## 月間ユニーク訪問者数

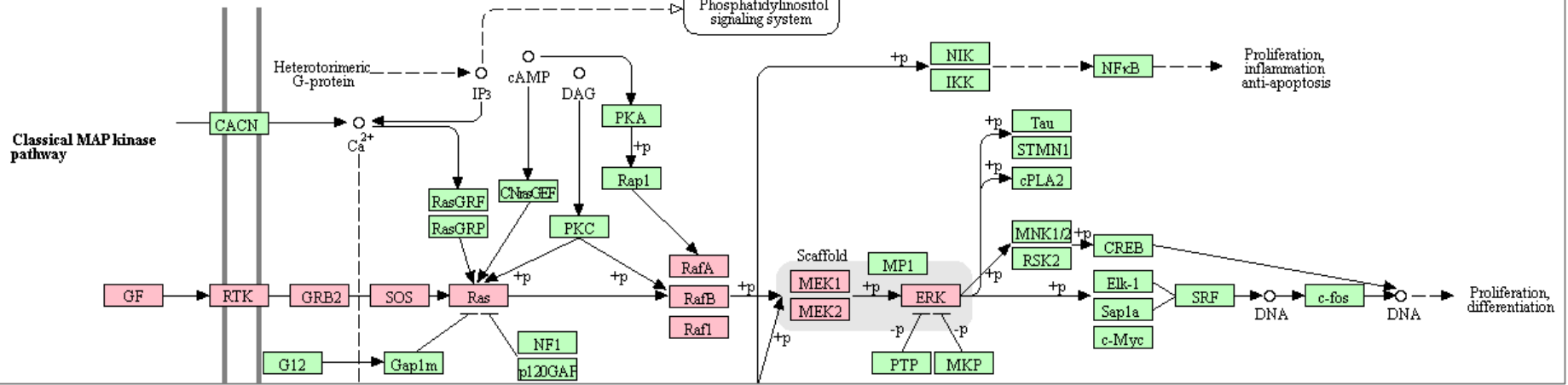


# KEGG NETWORK

Linking disease-related gene variants to network elements



MAPK SIGNALING PATHWAY



N00001	EGF	→ EGFR	→ GRB2 → SOS	→ RAS	→ RAF	→ MEK → ERK → CCND 1
N00276	EGF*	→ EGFR	→ GRB2 → SOS	→ RAS	→ RAF	→ MEK → ERK
N00229	TGFA	→ EGFR	→ GRB2 → SOS	→ RAS	→ RAF	→ MEK → ERK
N00230	TGFA*	→ EGFR	→ GRB2 → SOS	→ RAS	→ RAF	→ MEK → ERK
N00277	EREG	→ EGFR	→ GRB2 → SOS	→ RAS	→ RAF	→ MEK → ERK
N00278	EREG*	→ EGFR	→ GRB2 → SOS	→ RAS	→ RAF	→ MEK → ERK
N00279	AREG	→ EGFR	→ GRB2 → SOS	→ RAS	→ RAF	→ MEK → ERK
N00280	AREG*	→ EGFR	→ GRB2 → SOS	→ RAS	→ RAF	→ MEK → ERK
N00014	EGFR*	→ GRB2 → SOS	→ RAS	→ RAF	→ MEK → ERK → CCND 1	
N00006	EGFR*	→ GRB2 → SOS	→ RAS	→ RAF	→ MEK → ERK	
N00041	EGFR*	→ GRB2 → SOS	→ RAS	→ RAF	→ MEK → ERK	
N00021	EGF	→ (ERBB2+EGFR)	→ GRB2 → SOS	→ RAS	→ RAF	→ MEK → ERK
N00022	EGF	→ (ERBB2*+EGFR)	→ GRB2 → SOS	→ RAS	→ RAF	→ MEK → ERK
N00252	EGF	→ (ERBB2*+EGFR)	→ GRB2 → SOS	→ RAS	→ RAF	→ MEK → ERK
N00015	PDGF	→ PDGFR	→ GRB2 → SOS	→ RAS	→ RAF	→ MEK → ERK
N00016	PDGF*	→ PDGFR	→ GRB2 → SOS	→ RAS	→ RAF	→ MEK → ERK
N00018	PDGFR*	→ GRB2 → SOS	→ RAS	→ RAF	→ MEK → ERK	
N00215	KITLG	→ KIT	→ GRB2 → SOS	→ RAS	→ RAF	→ MEK → ERK
N00003	KIT*	→ GRB2 → SOS	→ RAS	→ RAF	→ MEK → ERK	
N00019	FGF	→ FGFR	→ GRB2 → SOS	→ RAS	→ RAF	→ MEK → ERK
N00020	FGFR*	→ GRB2 → SOS	→ RAS	→ RAF	→ MEK → ERK	
N00011	FGFR3*	→ GRB2 → SOS	→ RAS	→ RAF	→ MEK → ERK → MSK1 → MYC	
N00217	FLT3LG	→ FLT3	→ GRB2 → SOS	→ RAS	→ RAF	→ MEK → ERK
N00004	FLT3*	→ GRB2 → SOS	→ RAS	→ RAF	→ MEK → ERK	

# KEGG NETWORK 開発 進捗状況

2017年12月 最初のバージョンとしてがんのネットワークを公開  
2018年5月 内分泌・代謝のネットワークを公開  
2018年8月 ウイルスのネットワークを公開

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Reference network elements	109
<hr/>	
Variant network elements	
caused by gene variants	185
caused by viruses	145
caused by drugs	9
<hr/>	
Total	448

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As of August 21, 2018

# KEGG NETWORK: Cancer Networks

06201 Signaling network  
06210 MAPK (ERK) signaling  
06211 MAPK (JNK) signaling  
06212 MAPK (p38) signaling  
06213 Other RAS signaling  
06214 PI3K signaling  
06215 WNT signaling  
06216 NOTCH signaling  
06217 HH signaling  
06218 TGFB signaling  
06219 JAK-STAT signaling  
06220 Calcium signaling  
06221 TLR signaling  
06222 IFN signaling  
06223 TNF-NFKB signaling  
06224 CXCR signaling  
06225 HIF-1 signaling  
06226 KEAP1-NRF2 signaling  
06227 NR signaling  
06229 MHC presentation  
06228 Autophagy  
06230 Cell cycle G1/S  
06231 Apoptosis  
06232 Telomerase activity

06202 Transcription  
06240 All cancer types  
06241 Leukemia and lymphoma  
06242 Carcinoma  
06243 Sarcoma  
06244 Other

## Cancer Types

Gastric cancer  
Pancreatic cancer  
Hepatocellular carcinoma  
Renal cell carcinoma  
Bladder cancer  
Non-small cell lung cancer  
Small cell lung cancer  
Melanoma  
Basal cell carcinoma  
Breast cancer  
Endometrial cancer  
Prostate cancer  
Glioma  
Thyroid cancer  
Acute myeloid leukemia  
Chronic myeloid leukemia



# KEGG NETWORK

## Endocrine Networks

06301 CRH-ACTH-Cortisol network  
06310 ACTH-cortisol signaling  
06311 CRH-ACTH signaling  
06312 EGFR-ERK-ACTH signaling  
06313 NR-CYP regulation  
06314 Cortisol biosynthesis  
06315 Cortisol transport  
06302 Aldosterone network  
06316 Angiotensin-aldosterone signaling  
06303 Parathyroid hormone network  
06317 PTH-cAMP-PKA signaling  
06318 CaSR-PTH signaling  
06304 Aryl hydrocarbon receptor network  
06319 AHR-cell cycle regulation  
06305 Cholesterol network  
06320 APOB-LDLR signaling

## Virus Networks

06101 Signaling network (virus)  
06110 MAPK signaling (virus)  
06111 PI3K signaling (virus)  
06112 WNT signaling (virus)  
06113 NOTCH signaling (virus)  
06114 JAK-STAT signaling (virus)  
06115 Calcium signaling (virus)  
06116 TLR signaling (virus)  
06117 CGAS-STING signaling (virus)  
06127 Complement activation (virus)  
06118 IFN signaling (virus)  
06119 TNF signaling (virus)  
06120 Chemokine signaling (virus)  
06121 MHC presentation (virus)  
06122 Autophagy (virus)  
06123 Cell cycle (virus)  
06124 Apoptosis (virus)  
06125 Cytoskeletal regulation (virus)

# Viral Oncoprotein

KSHV (Kaposi sarcoma-associated herpesvirus) K1 protein

hsa05167

N00160	kshvK1	→ RAS	→ RAF	→ MEK	→ ERK				
N00159	kshvK1	→ PI3K	→ PIP3	→ AKT	→ MTOR				
N00179	kshvK1	→ PI3K	→ PIP3	→ AKT	→ IKK	→ NFKBIA	→ NFKB	→ VEGFA	
N00180	kshvK1	→ PLCG2	→ IP3	→ Ca <sup>2+</sup>	→ CALM	- CN	→ NFAT		

EML4-ALK fusion gene in colorectal cancer

hsa05223

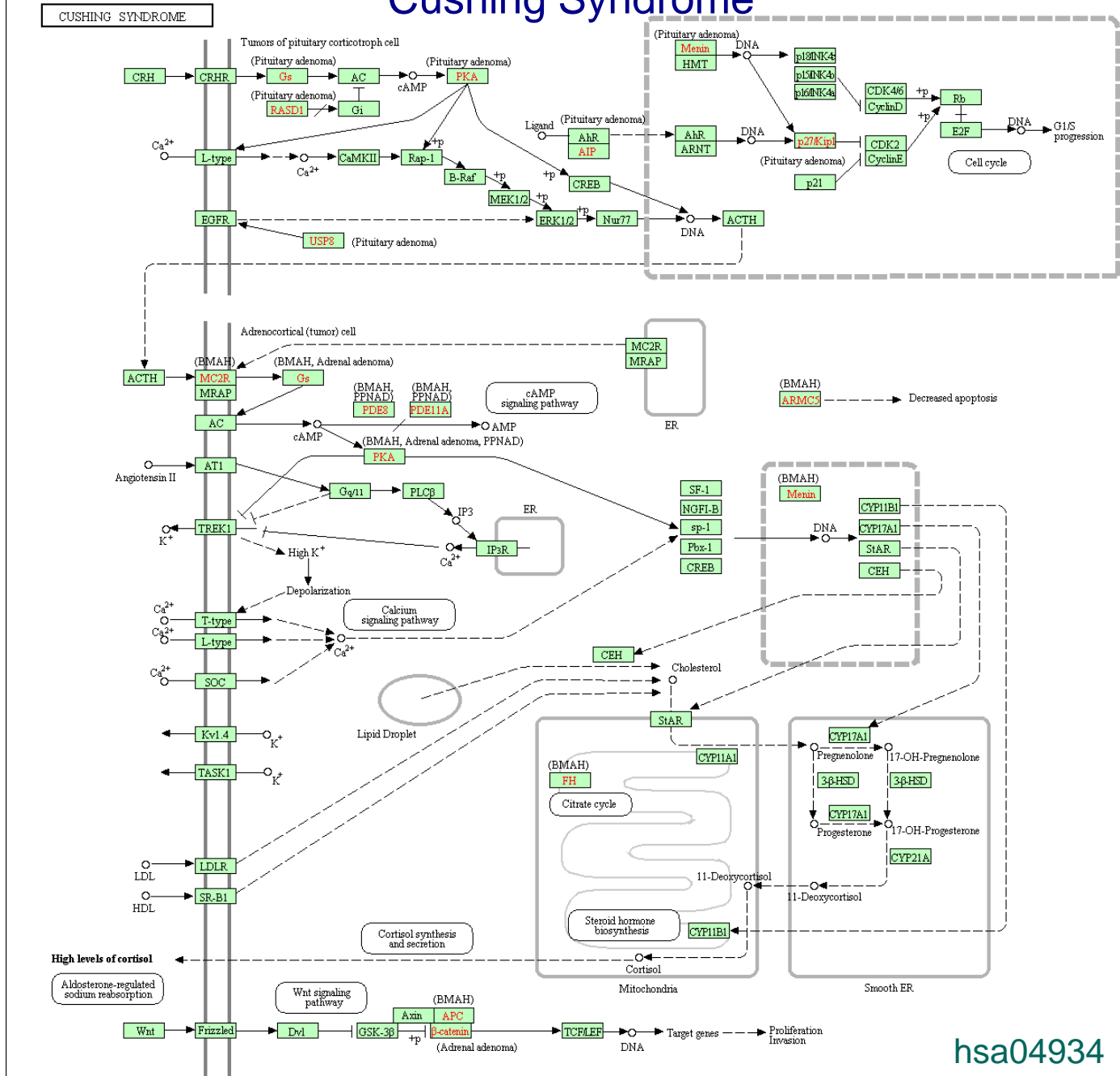
N00007	EML4-ALK	→ RAS	→ RAF	→ MEK	→ ERK	→ CCND1			
N00025	EML4-ALK	→ PLCG	→ (Ca <sup>2+</sup> ,DAG)	→ PKC	→ RAF	→ MEK	→ ERK	→ CCND1	
N00047	EML4-ALK	→ PI3K	→ PIP3	→ AKT	→ BAD				
N00105	EML4-ALK	→ JAK3	→ STAT3,STAT5						



# Cushing Syndrome

CRH 視床下部  
 ↓  
 ACTH 下垂体  
 ↓  
 Cortisol 副腎

ACTH 依存性  
 ACTH 非依存性



# Endocrine Network

## CRH-ACTH-Cortisol network

nt06301

N00297	ACTH	→ (MC2R+MRAP)	→ GNAS	→ ADCY	→ cAMP	→ PKA	→ (NR5A1,NR4A1,SP1,P..	⇒ (STAR,CYP11B1)	→ Cortisol
N00299	ACTH	≠ (MC2R*+MRAP)	≠ GNAS						
N00300	ACTH	≠ (MC2R+MRAP*)	≠ GNAS						
N00321			GNAS*	→ ADCY	→ cAMP	→ PKA	→ (NR5A1,NR4A1,SP1,P..	⇒ (STAR,CYP11B1)	→ Cortisol
N00323				(PDE11A*,PDE8B*)	≠ cAMP	→ (PRKAR1A+PRKACA)	→ (NR5A1,NR4A1,SP1,P..	⇒ (STAR,CYP11B1)	→ Cortisol
N00320						PRKACA*	→ (NR5A1,NR4A1,SP1,P..	⇒ (STAR,CYP11B1)	→ Cortisol
N00322						(PRKAR1A*+PRKACA)	→ (NR5A1,NR4A1,SP1,P..	⇒ (STAR,CYP11B1)	→ Cortisol
N00298	ACTH	→ (MC2R+MRAP)	→ GNAS	→ ADCY	→ cAMP	→ PKA	→ (NR5A1,NR4A1,SP1,P..	⇒ CYP11B2*	→ Aldosterone
N00324	CRH	→ CRHR	→ GNAS	→ ADCY	→ cAMP	→ PKA	→ CREB	→ ACTH	
N00325		RASD1*	≠ GNAI	≠ ADCY	→ cAMP	→ PKA	→ CREB	→ ACTH	
N00326			GNAS*	→ ADCY	→ cAMP	→ PKA	→ CREB	→ ACTH	
N00327	CRH	→ CRHR	→ GNAS	→ ADCY	→ cAMP	→ (PRKAR1A*+PRKACA)	→ CREB	→ ACTH	
N00318						EGFR	→ ERK1/2	→ ACTH	
N00319					USP8*	→ EGFR	→ ERK1/2	→ ACTH	
N00306					NROB1	≠ NR5A1	⇒ (CYP11B1,CYP17A1)		
N00307					NROB1*	≠ NR5A1	⇒ (CYP11B1,CYP17A1)		
N00308					NROB1	≠ NR5A1*	≠ (CYP11B1,CYP17A1)		
N00339	Cholesterol	- CYP11A1	→ Pregnenolone	- (HSD3B+CYP21A2+CYP..	→ Aldosterone				
N00338	Cholesterol	- CYP11A1	→ Pregnenolone	- (HSD3B+CYP17A1+CYP..	→ Cortisone	- HSD11B	→ Cortisol		
N00309					(Cortisone+NADPH)	- HSD11B	→ (Cortisol+NADP+)		
N00310					Cortisone	≠ HSD11B1*	≠ Cortisol		
N00311			NADP	- H6PD	→ NADPH				
N00312			NADP	≠ H6PD*	≠ NADPH				
N00313						SERPINA6	- Cortisol		
N00314						SERPINA6*	≠ Cortisol		

## Cushing's syndrome

H01431

N00321			GNAS*	→ ADCY	→ cAMP	→ PKA	→ (NR5A1,NR4A1,SP1,P..	⇒ (STAR,CYP11B1)	→ Cortisol
N00323				(PDE11A*,PDE8B*)	≠ cAMP	→ (PRKAR1A+PRKACA)	→ (NR5A1,NR4A1,SP1,P..	⇒ (STAR,CYP11B1)	→ Cortisol
N00320						PRKACA*	→ (NR5A1,NR4A1,SP1,P..	⇒ (STAR,CYP11B1)	→ Cortisol
N00322						(PRKAR1A*+PRKACA)	→ (NR5A1,NR4A1,SP1,P..	⇒ (STAR,CYP11B1)	→ Cortisol
N00325		RASD1* ≠	GNAI	≠ ADCY	→ cAMP	→ PKA	→ CREB	→ ACTH	
N00326			GNAS*	→ ADCY	→ cAMP	→ PKA	→ CREB	→ ACTH	
N00327	CRH	→ CRHR	→ GNAS	→ ADCY	→ cAMP	→ (PRKAR1A*+PRKACA)	→ CREB	→ ACTH	
N00319					USP8*	→ EGFR	→ ERK1/2	→ ACTH	
N00315	AIP* ≠	AHR							
N00290			(MEN1*+KMT2A) ≠	(CDKN1B,CDKN2C)					
N00316				CDKN1B*	≠ (CCNE+CDK2)	→ RB1	≠ E2F		



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Target-based classification of drugs

▼ ▼ ▼ ▼ ▼  One-click mode

▶ **G Protein-coupled receptors**

▶ **Ion channels**

▶ **Nuclear receptors**

▼ **Protein kinases**

- ▶ Serine/threonine kinases
- ▶ Receptor serine/threonine kinases (RSTK)
- ▼ Receptor tyrosine kinases (RTK)
  - ▶ EGFR family
  - ▶ INSR family
  - ▶ PDGFR family
  - ▶ FGFR family
  - ▶ VEGFR family
  - ▶ MET family
  - ▶ TRK family
  - ▶ EPH family
  - ▶ AXL family
  - ▼ ALK family
    - ▶ ALK (CD246) [HSA:238] [KO:K05119]
    - ▼ EML4-ALK [HSA\_VAR:238v1] [HSA:238] [KO:K05119]
      - D09731 Crizotinib (JAN/USAN/INN) <JP/US>
    - ▼ EML4-ALK [HSA\_VAR:238v2] [HSA:238] [KO:K05119]
      - D10551 Ceritinib (JAN/USAN/INN) <JP/US>
      - D10450 Alectinib hydrochloride (JAN) <JP/US>
      - D10866 Brigatinib (USAN) <US>
  - ▶ TIE family
  - ▶ RET family
- ▶ Non-receptor tyrosine kinases

▶ **Cytokines and receptors**

▶ **Cell surface molecules and ligands**

▶ **Transporters**

▶ **Enzymes**

▶ **Not elsewhere classified**

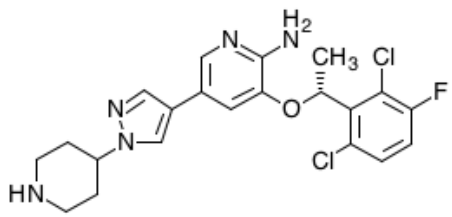
```

N10003 Crizotinib
      ↓
N00007 EML4-ALK → RAS → RAF → MEK → ERK → CCND 1
N10003 Crizotinib
      ↓
N00025 EML4-ALK → PLCG → (Ca2+,DAG) → PKC → RAF → MEK → ERK → CCND 1
N10003 Crizotinib
      ↓
N00047 EML4-ALK → PI3K → PIP3 → AKT → BAD
N10003 Crizotinib
      ↓
N00105 EML4-ALK → JAK3 → STAT3,STAT5
  
```

```

N10004 (Alectinib,Ceritinib,Brigatinib)
      ↓
N00007 EML4-ALK → RAS → RAF → MEK → ERK → CCND 1
N10004 (Alectinib,Ceritinib,Brigatinib)
      ↓
N00025 EML4-ALK → PLCG → (Ca2+,DAG) → PKC → RAF → MEK → ERK → CCND 1
N10004 (Alectinib,Ceritinib,Brigatinib)
      ↓
N00047 EML4-ALK → PI3K → PIP3 → AKT → BAD
N10004 (Alectinib,Ceritinib,Brigatinib)
      ↓
N00105 EML4-ALK → JAK3 → STAT3,STAT5
  
```

br08310

Entry	D09731 Drug
Name	Crizotinib (JAN/USAN/INN); Xalkori (TN)
Product	XALKORI (Pfizer Laboratories Div Pfizer)
Formula	C21H22Cl2FN5O
Exact mass	449.1185
Mol weight	450.3367
Structure	 <p>D09731</p> <p><a href="#">Mol file</a> <a href="#">KCF file</a> <a href="#">DB search</a></p>
Class	Enzyme inhibitor DG02892 CYP2B6 inhibitor Transporter inhibitor DG01622 ABCB1 (P-GP) inhibitor DG02863 SLC22A2 (OCT2) inhibitor
Remark	Therapeutic category: 4291 ATC code: L01XE16 Product: D09731<JP/US>
Efficacy Disease	Antineoplastic, Tyrosine kinase inhibitor Non-small cell lung cancer (ALK or ROS1-positive) [DS:H00014]
Target	EML4-ALK [HSA_VAR:238v1] [HSA:238] [KO:K05119] ROS1* [HSA_VAR:6098v1] [HSA:6098] [KO:K05088]
Network Pathway	N10003 First-generation tyrosine kinase inhibitor to ALK fusi hsa05200 Pathways in cancer hsa05223 Non-small cell lung cancer
Metabolism	Enzyme: CYP3A4 [HSA:1576], CYP3A5 [HSA:1577]
Interaction	CYP inhibition: CYP2B6 [HSA:1555] Transporter inhibition: ABCB1 [HSA:5243], SLC22A1 [HSA:6580], S [HSA:6582] <a href="#">DDI search</a>
Structure map	map07045 Antineoplastics - protein kinases inhibitors

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ICD-11 による疾患分類

Go

▼ ▼ ▼ ▼ ▼ ▼ ▼ ▼  One-click mode

- ▼ 01 Certain infectious or parasitic diseases
  - ▼ Gastroenteritis or colitis of infectious origin
    - ▼ Bacterial intestinal infections
      - ▼ 1A00 Cholera
        - H00110 コレラ
      - ▼ 1A01 Intestinal infection due to other Vibrio
        - H00307 腸炎ビブリオ感染症
        - H00308 ビブリオ・バルニフィカス感染症
      - ▼ 1A02 Intestinal infections due to Shigella
        - H00299 細菌性赤痢
      - ▼ 1A03 Intestinal infections due to Escherichia coli
        - H00278 腸管病原性大腸菌感染症
        - H00280 腸管毒素病原性大腸菌感染症
        - H01311 腸管組織侵襲性大腸菌感染症
        - H00277 腸管出血性大腸菌感染症
        - H01312 腸管凝集性大腸菌感染症
      - ▼ 1A04 Enterocolitis due to Clostridium difficile
        - H00338 偽膜性大腸炎
      - ▼ 1A05 Intestinal infections due to Yersinia enterocolitica
        - H00298 エルシニア感染症
      - ▼ 1A06 Gastroenteritis due to Campylobacter
        - H00321 カンピロバクター感染症
      - ▼ 1A07 Typhoid fever
        - H00111 腸チフス
      - ▼ 1A08 Paratyphoid Fever
        - H00112 パラチフス
      - ▼ 1A09 Infections due to other Salmonella
        - H00113 サルモネラ感染症
      - ▼ 1A0Y Other specified bacterial intestinal infections
        - H01454 結腸スピロヘータ症
      - 1A0Z Bacterial intestinal infections, unspecified
    - ▼ Bacterial foodborne intoxications
      - ▼ 1A10 Foodborne staphylococcal intoxication
        - H01175 ブドウ球菌感染症
      - ▼ 1A11 Botulism
        - H00339 ボツリヌス中毒症
      - ▼ 1A12 Foodborne Clostridium perfringens intoxication
        - H00335 ウェルシュ菌食中毒
      - ▼ 1A13 Foodborne Bacillus cereus intoxication
        - H00329 セレウス菌食中毒
      - ▼ 1A1Y Other specified bacterial foodborne intoxications
        - H00300 エンテロバクター感染症
      - 1A1Z Bacterial foodborne intoxications, unspecified

## 今年度の達成目標・タスク

達成目標	タスク	進捗状況
内分泌代謝疾患に関連するネットワーク要素と遺伝子バリエーションのデータベース化	<ul style="list-style-type: none"><li>・ 文献調査</li><li>・ データ入力</li></ul>	公開済み データ追加予定
ウイルスによる免疫系などの模倣ネットワーク要素のデータベース化	<ul style="list-style-type: none"><li>・ 文献調査</li><li>・ データ入力</li></ul>	公開済み データ追加予定
ネットワーク可視化とマッピングツールの開発	<ul style="list-style-type: none"><li>・ Cancer Network Viewerのマッピング機能開発</li><li>・ ネットワークバリエーションマップのマッピング機能開発とKEGG Mapperへの組み込み</li></ul>	Drug-target表示機能、検索機能強化開発済み マッピング機能開発中