

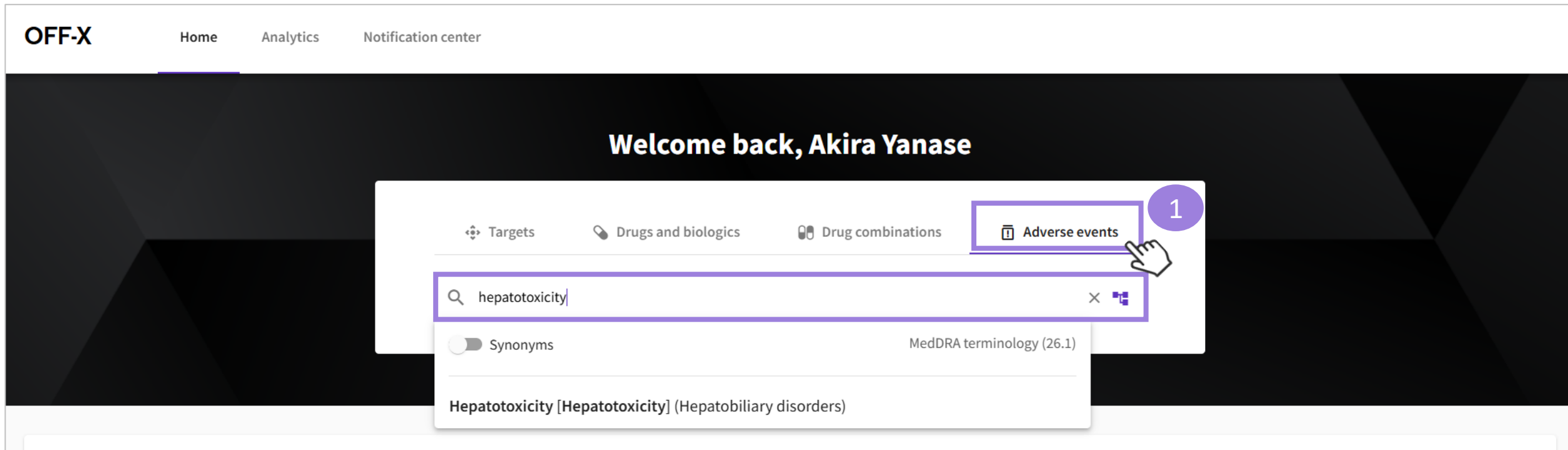
OFF-X

Structure-toxicity explorer/Comparative table builder/ Pathway mapsを活用した毒性・安全性情報の調査活用事例

本事例では肝毒性を例に、毒性が特定の構造由来のものであるかの検証、またターゲットの作用との関連性がエビデンス上、高いとされるMOAをリスト化し、毒性発現を考察する事例をご紹介します。

1. 肝毒性(Hepatotoxicity)と関連して報告のあるターゲットやドラッグを検索する

- ① TOP画面の「Adverse events」をクリックし、検索ボックスに「hepatotoxicity」を入力し検索



2. 肝毒性が多く報告されているドラッグをリスト化

- ① Drugs and biologicsの「Master view」をクリックし、肝毒性が報告されているドラッグをリスト化。
- ② Drugs alertsをクリックし報告件数の多い順に並び替え。
- ③ 例えば、「isoniazid」に注目し、クリックする

OFF-X

HomeAnalyticsNotification center

Adverse events

Type adverse event or MedDRA PT code and select

Adverse event

Hepatotoxicity

Comparative table builder

Targets

Drugs and biologics

Master view

Translational safety

Filter

Columns

Drug/combination • Highest phase

OFF-X Drug Score

Classifier tags

Frequency in clinical trials

Number of alerts

Alert type

Alert phase

Text mining FDA SBA

Drug/combination • Highest phase	OFF-X Drug Score	Classifier tags	Frequency in clinical trials	Number of alerts	Alert type	Alert phase	Text mining FDA SBA
methotrexate • Small molecule • Launched	Very high	CausalitySeverityPharmacogenomics	≥0.01 - <0.1%	108	108	PreclinicalClinical	
acetaminophen • Small molecule • Launched	High	CausalitySeverityPharmacogenomics		77	67	PreclinicalClinical	
nivolumab • Biologic • Launched	Medium	CausalitySeverityPharmacogenomics		55	48	PreclinicalClinical	
azathioprine • Small molecule • Launched	High	CausalitySeverityPharmacogenomics		48	42	PreclinicalClinical	
pazopanib • Small molecule • Launched	Very high	CausalitySeverityPharmacogenomics	≥1 - <10%	58	42	PreclinicalClinical	
crizotinib • Small molecule • Launched	Very high	CausalitySeverityPharmacogenomics		60	41	PreclinicalClinical	
isoniazid • Small molecule • Launched	High	CausalitySeverityPharmacogenomics		38	38	PreclinicalClinical	

3. 注目した化合物から構造検索を行う

- ① 「Snapshot」をクリックし、isoniazidの構造を確認
- ② 肝毒性が特定の構造に関連があるかを確認するため「Structure-toxicity explorer」をクリック
- ③ 例えば「Substructure(部分一致)」を選択し、検索

The screenshot displays the OFF-X web application interface. The main header includes 'OFF-X', 'Home', 'Analytics', and 'Notification center'. The left sidebar shows 'Drug isoniazid' with a 'Snapshot' button highlighted by a hand icon and a purple circle labeled '1'. Below this, a 'Structure-toxicity explorer' button is highlighted by a hand icon and a purple circle labeled '2'. A purple arrow points from this button to a modal window titled 'Upload or draw a structure'. In this modal, the 'Substructure' button is highlighted by a hand icon and a purple circle labeled '3'. The modal also contains 'Exact structure' and 'Similarity' buttons, a chemical structure editor toolbar, and a search bar with a 'Search' button highlighted by a hand icon. The main content area shows the 'Drug type' as 'Small Molecule', 'Highest phase' as 'Launched 1952', and 'Drug names (3)' as 'isoniazid sodium methanesulfonate hydrate', 'Nydrazid', and 'Rimifon'. A chemical structure of isoniazid is shown below the 'Structure-toxicity explorer' button.

OFF-X Home Analytics Notification center

Drug isoniazid

Snapshot Safety alerts Drug safety profile Comparative views

Structure-toxicity explorer

Copy Smiles

Drug type Small Molecule

Highest phase Launched 1952

Drug names (3)

isoniazid sodium methanesulfonate hydrate

Nydrazid

Rimifon

Upload or draw a structure

Substructure Exact structure Similarity

Search

Clear

4. 似た構造をもつ化合物の肝毒性に関する報告を確認

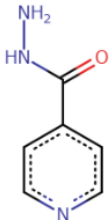
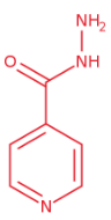
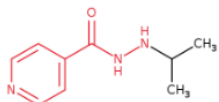
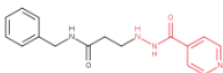
- ① Structure-toxicity explorerにより、似た構造をもつ化合物の肝毒性に関する報告の確認が可能。毒性が特定の構造由来のものかどうかの検証を進める一助としてご利用いただけます。

OFF-X Home Analytics Notification center Drugs and biologics Type drug and select

Structure-toxicity explorer

Comparing 4 structures

Filter Hide drugs View AE/SOC Sort drugs Similarity Table Heat map

					
Adverse event • System Organ Class	100% similarity MW: 137.1 isoniazid Launched 1952	75% similarity MW: 179.2 iproniazid	62% similarity MW: 323.1 IQG-607	49% similarity MW: 298.3 nialamide	
Hepatotoxicity • Hepatobiliary disorders					
Hyperbilirubinaemia • Hepatobiliary disorders					
Jaundice • Hepatobiliary disorders					
Nausea • Gastrointestinal disorders					
Nervous system disorder • Nervous system disorders					

Tools

5. 肝毒性に関してターゲットの作用との関連性がエビデンス上、高いとされるMOAをリスト化

- ① P.3の2. と同様にTargetsから「Master view」をクリック
- ② OFF-X Target/Class Scoreからエビデンスが高いとされるMOAを確認
例えば、「30S ribosomal protein」「COX-2」「PI3Kgamma」に注目
- ③ 「Comparative table builder」をクリック

OFF-X

HomeAnalyticsNotification center

Adverse events

Type adverse event or MedDRA PT code and select

Adverse event

Hepatotoxicity

1

TargetsDrugs and biologics

Master view

Translational safety

FilterColumns

2

30S ribosomal protein • Inhibitors

Amidophosphoribosyltransferase • Inhibitors

COX-2 • Inhibitors

PI3Kgamma • Inhibitors

PPARgamma • Modulators

ABL1 • Inhibitors

3

Comparative table builder

Target • Action	OFF-X Target/Class Score	Classifier tags	Number of alerts	Alert type	Alert phase							
				Class alerts	Drug alerts	Preclinical	Clinical					
30S ribosomal protein • Inhibitors	Very high	CausalitySeverity	33	14	6	4	27	12	4	4	29	11
Amidophosphoribosyltransferase • Inhibitors	Very high	CausalitySeverityPharmacogenomics	65	2	6	1	59	2	3	2	62	2
COX-2 • Inhibitors	Very high	CausalitySeverityPharmacogenomics	165	53	10	14	155	53	61	20	104	46
PI3Kgamma • Inhibitors	Very high	On-TargetCausalitySeverity	16	3	3	1	13	3	2	1	14	3
PPARgamma • Modulators	Very high	On-TargetCausalitySeverityPharmacogenomics	53	10	5	0	48	10	19	4	34	9
ABL1 • Inhibitors	High	CausalitySeverityPharmacogenomics	87	8	2	3	85	8	8	5	79	8

6. 肝毒性に関してターゲットの作用との関連性がエビデンス上、高いとされるMOAをリスト化

- ① 注目したMOAを同時に条件設定し、「Build table」をクリック
- ② 「Filter」をクリックし、System Organ Classに「Hepatobiliary disorders」を入力し、「Apply」をクリック
- ③ 作用別にその他の肝障害における報告件数を一覧確認することで、ターゲットへの作用とそのほかの肝障害発現における関連性の考察をサポート

OFF-X

Home

Analytics

Notification center

Comparative table builder

< Targets

Type target, gene or UniProt ID and select

Add all drugs acting on the selected target-actions

Selected target-actions

Remove 3

PI3Kgamma

Inhibitors

COX-2

Inhibitors

30S ribosomal protein

Inhibitors

1

Build table

Filter

Adverse event filters

Adverse event | System Organ Class | SMQ

Safety alert filters

Classifier tags

Clinical trial ID | Patient condition | Patient population

Alert type

Alert phase | Species

Source type

Association based on reference

Genetic studies/variants

Time period

Adverse event

Hepatobiliary disorders

SMQ

Designated Medical Events

FDA

And

Or

EMA

Clear all filters

Cancel

Apply

OFF-X

Home

Analytics

Notification center

Comparative table builder

2

Filter

3

Adverse event | System Organ Class | SMQ (1)

Clear all filters

Adverse event • System Organ Class

30S ribosomal protein inhibitors

COX-2 inhibitors

PI3Kgamma inhibitors

Hepatotoxicity • Hepatobiliary disorders	33	165	16
Hepatic failure DME • Hepatobiliary disorders	14	71	2
Hepatitis • Hepatobiliary disorders	11	76	3
Drug-induced liver injury DME • Hepatobiliary disorders	40	130	
Hepatic function abnormal • Hepatobiliary disorders	16	51	1
Jaundice • Hepatobiliary disorders	13	72	
Liver disorder • Hepatobiliary disorders	13	63	2
Hyperbilirubinaemia • Hepatobiliary disorders	8	6	
Cholestasis • Hepatobiliary disorders	6	14	
Autoimmune hepatitis DME • Hepatobiliary disorders	28	14	

7. 肝毒性報告の多いターゲットについて、Pathway Mapsを活用して毒性発現を考察

- ① Comparative table builder中の「COX-2」をクリック
- ② 「Biological context」をクリックし、Pathway mapsの一覧を表示
- ③ 「Angiogenesis in hepatocellular carcinoma (HCC)」をクリック

OFF-X Home Analytics Notification center

Comparative table builder

Edit table Filter View AE/SOC Heat map Number of alerts

Adverse event | System Organ Class | SMQ (1) Clear all filters

Adverse event • System Organ Class	30S ribosom... Inhibitors	COX-2 Inhibitors	PI3Kgamma Inhibitors
Hepatotoxicity • Hepatobiliary disorders	33	165	16
Hepatic failure DME • Hepatobiliary disorders	14	71	2
Hepatitis • Hepatobiliary disorders	11	76	3
Drug-induced liver injury DME • Hepatobiliary disorders	40	130	
Hepatic function abnormal • Hepatobiliary disorders	16	51	1
Jaundice • Hepatobiliary disorders	13	72	
Liver disorder • Hepatobiliary disorders	13	63	2
Hyperbilirubinaemia • Hepatobiliary disorders	8	6	
Cholestasis • Hepatobiliary disorders	6	14	
Autoimmune hepatitis DME • Hepatobiliary disorders	28	14	

OFF-X Home Analytics Notification center

Targets Type target or gene or UniProt ID and select

Target COX-2

Comparative table builder Keep me posted

Snapshot Safety alerts Target safety profile Comparative views Biological context

Pathway maps

All Pathological Physiological

Activation of TNF-alpha-dependent pro-tumoral effect in colorectal cancer

Aminoglycoside- and cisplatin-induced hair cell death in

Angiogenesis in hepatocellular carcinoma (HCC)

Apoptosis and survival_Endoplasmic reticulum stress response

Apoptosis and survival_FasL(TNFSF6)/ FasR(CD95)-induced cell death

Arachidonic acid metabolites production in alveolar macrophages in asthma

8. Pathway Mapsを活用して毒性発現を考察

- ① 「Description」をクリックしPathway maps全体についての概要を確認
- ② PathwayにおけるCOX-2の位置づけを確認
- ③ 「COX-2」をクリックすることで周囲のターゲットとの相互作用情報の確認が可能

OFF-X Home Analytics Notification center Targets

Pathway maps

Angiogenesis in hepatocellular carcinoma (HCC)

Default Safety alerts **Description** Legend

1

2

3

Description

Abstract Details Sources

HIF1A is expressed in HCC [1] and induces angiogenesis via **VEGF-A**. Expression of **HIF1A** is a prognostic factor for recurrence after curative resection [2]. **VEGF-A**, overexpressed in HCC [3], [4] also is induced by hypoxia-activated **HIF1A** (see response to hypoxia) [5].

Expression of **Angiopoietin 1** and **TIE2** is not significantly altered in HCC compared to normal tissues [3], [6]. **Angiopoietin 2** is overexpressed in HCC, which correlates with angiogenesis. The initiation of angiogenesis by **Angiopoietin 2** is positively correlates with **VEGF-A** signaling [2], [3], [4], [5], [6], [7], [8], [9]. **Angiopoietin 2** synergize with **VEGF-A** to induce **MMP-2** and **MMP-9** [10]. Expression of **Angiopoietin 1** and **Angiopoietin 2** in HCC is not induced by hypoxia [5] and **Angiopoietin 2** can be a prognostic factor for recurrence after curative resection [2].

IGF-2 via **HIF1A** / **VEGF-A** induces angiogenesis [11], [12], [13].

Hepatitis B virus **X protein (HBV-C)** induces stabilization and activation of **HIF1A**. **HIF1A** activation leads to expression of **VEGF-A** and angiogenesis, contributing to cancer progression [14], [15].

ID1 in HCC enhances the stability of **HIF1A** and, thus, enhances expression of **VEGF-A** [16].

Securin is overexpressed in HCC and promotes expression of **FGF2**. The latter induces expression of **VEGF-A** in endothelial cells, followed up by angiogenesis [17], [18], [19].

Support

Build comparative table

COX-2 (PTGS2)
Enzyme
Highest Phase: Launched
17972 Safety Alerts 3036 Serious/severe safety alerts

Showing 1 interaction

From	Mechanism	To
COX-2 (PTGS2)	Catalysis	1.14.99.1

参考 Structure-toxicity explorer[※]/Comparative table builder/ Pathway mapsはTOP画面> Analyticsからのアクセスも可能

※旧Chemistry Dashboardがリニューアルし、Structure-toxicity explorerとして利用できるようになりました。このツールを利用して構造に基づいたドラッグの毒性・安全性情報を検索し、毒性・安全性プロファイルにおける化学構造の役割を評価する一助となります。

The screenshot displays the OFF-X Analytics dashboard. At the top, there is a navigation bar with 'OFF-X', 'Home', 'Analytics' (highlighted with a purple box and a hand cursor), and 'Notification center'. To the right of the navigation bar is a search bar labeled 'Targets' with a dropdown arrow and a search icon, with the placeholder text 'Type target or gene or UniProt ID and select'. Below the navigation bar, the main section is titled 'Data in action to de-risk your R&D programs'. This section contains a row of buttons: 'All use cases' (highlighted with a purple box), 'Target safety assessment', 'Toxicity exploration', 'Secondary pharmacology profiling', 'Preclinical to clinical translation', 'Structure-toxicity assessment', 'Mechanistic toxicity evaluation', 'Drug vs class assessment', and 'Safety profile benchmark'. Below this row, there are eight tool cards arranged in a 2x4 grid. The first card, 'Comparative table builder', is highlighted with a purple box and a hand cursor. The second card, 'Mounting evidence chart', is not highlighted. The third card, 'Pathway maps' (marked 'New'), is highlighted with a purple box and a hand cursor. The fourth card, 'Real-world evidence analysis', is not highlighted. The fifth card, 'Secondary pharmacology panels' (marked 'New'), is not highlighted. The sixth card, 'Structure-toxicity explorer' (marked 'New'), is highlighted with a purple box and a hand cursor. The seventh card, 'Translational safety', is not highlighted. The eighth card, 'Unexpected toxicity evaluation', is not highlighted. Each card contains an icon, a title, and a brief description of its function.

OFF-X Home **Analytics** Notification center

Targets

Data in action to de-risk your R&D programs

All use cases Target safety assessment Toxicity exploration Secondary pharmacology profiling Preclinical to clinical translation Structure-toxicity assessment Mechanistic toxicity evaluation Drug vs class assessment Safety profile benchmark

Safety risk evaluation

Comparative table builder
Anticipate safety issues of new compounds and combinations, benchmark drugs and targets and assess the mechanisms behind adverse events.

Mounting evidence chart
Discover and compare drug-safety trends to anticipate emerging concerns

Pathway maps ^{New}
Anticipate and understand safety issues of targets based on upstream or downstream genes in their signaling cascade

Real-world evidence analysis
Assess and validate potential pharmacovigilance signals to optimize risk management plans

Secondary pharmacology panels ^{New}
Explore an integrated view of safety-related targets to keep your in vitro panels updated

Structure-toxicity explorer ^{New}
Correlate chemical structures with safety liabilities.

Translational safety
Assess the correlation of safety insights of targets and drugs from discovery to clinical

Unexpected toxicity evaluation
Assess the mechanisms behind unpredicted adverse events

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- ※本キャンペーンは、予告なく変更または終了させていただく場合がございます。あらかじめご了承ください。

ドラッグレコード

OFF-X Home Analytics Notification center Drugs and biologics Type drug and select

Drug nivolumab Comparative table builder Keep me posted

Snapshot Safety alerts Drug safety profile Comparative views

Drug type	Highest phase	OFF-X drug ID
Biologic	Launched 2014	140816
Product category/modality	Drug names (8)	Organizations (6)
Cancer Immunotherapy	Nivolumab BMS	Amgen Inc.
Follow-on Products	Opdivo	Bristol-Myers Squibb Co.
Human Monoclonal Antibodies	Xdivane	Luye Pharma Group Ltd.
Monoclonal Antibodies	ABP-206	National Cancer Institute (NCI)
	BMS-936558	Ono Pharmaceutical Co., Ltd.
	LY-01015	Xbrane Biopharma AB
	MDX-1106	
	...	

Cortellis Drug Discovery Intelligence (4)
1243105, 421460, 1132935, 1049604

Cortellis Competitive Intelligence (2)
108155, 54804

DrugCentral (1)
nivolumab

ChEMBL (1)
CHEMBL2108738

Support

ターゲットレコード

OFF-X Home Analytics Notification center Targets Type target or gene or UniProt ID and sel

Target COX-2 / Inhibitors Comparative table builder Keep me posted

Snapshot Safety alerts Target safety profile Comparative views Biological context

Class	Superfamily	OFF-X target ID	UniProt ID (1)
Enzymes	Oxidoreductases	367	P35354
Aliases (11)	Family	Gene (1)	Cortellis Drug Discovery Intelligence (1) New
COX2	Acting on paired donors, with incorporation or reduction of molecular oxygen	PTGS2	G5743
Cyclooxygenase 2			MetaCore (1)
Cyclooxygenase-2			153
PGH synthase 2	Subfamily		
PGHS-2	Miscellaneous		
PHS II			
PTGS2			
...			

Support



Think forward™

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