Breakthrough Therapy originally born in Tsukuba

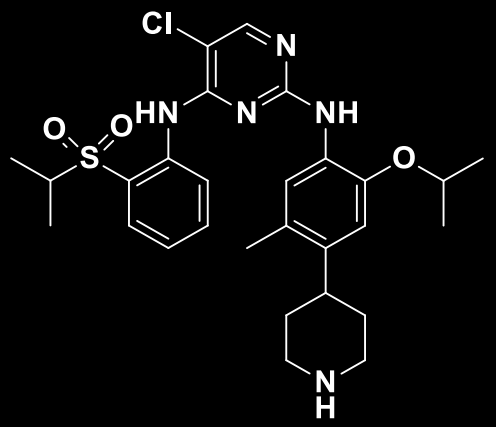
スイスNovartis社は3月15日、開発中の新規**ALK阻害剤LDK378**が、既治療のALK陽性非小細胞肺癌（NSCLC）の治療薬として、米食品医薬品局（FDA）よりBreakthrough Therapy（画期的な治療薬）の指定を受けたと発表した。

Breakthrough Therapyの指定は、重篤もしくは致命的な疾患の治療として、少なくとも1つの臨床的に重要な評価項目において既存の治療を超える改善が示された場合に、その薬の開発や審査を促進することを目的としている。

Breakthrough Therapy指定は、より強力なFDAガイダンスであり、ファーストラック制度の特徴をもつ。なお迅速承認制度や優先審査とは別の制度で、これらの制度の条件を満たしたときは、Breakthrough Therapy指定の治療薬でも迅速承認制度と優先審査は認められる。

LDK378は選択性の高いALK阻害剤。フェーズ1試験は、クリゾチニブ治療歴があったNSCLCを含む、ALK陽性進行癌患者88人を対象に行われた。この結果、ALK陽性NSCLC患者では顕著な抗腫瘍効果が認められ
＋PR＋未確定PR）は80%であった。

同社では2つのフェーズ2試験を進
している。試験の結果により、201



LDK378

Carlos Garcia-Echeverria, Takanori Kanazawa, Eiji Kawahara, Keiichi Masuya, Naoko Matsuura, Takahiro Miyake, Osamu Ohmori, Ichiro Umemura; 2, 4- di (phenylamino) pyrimidines useful in the treatment of neoplastic diseases, inflammatory and immune system disorders; WO2004080980 A1

LDK378 was assigned as Breakthrough Therapy Designation on March 2013

２０１４年４月２９日にFDAを承認を受ける

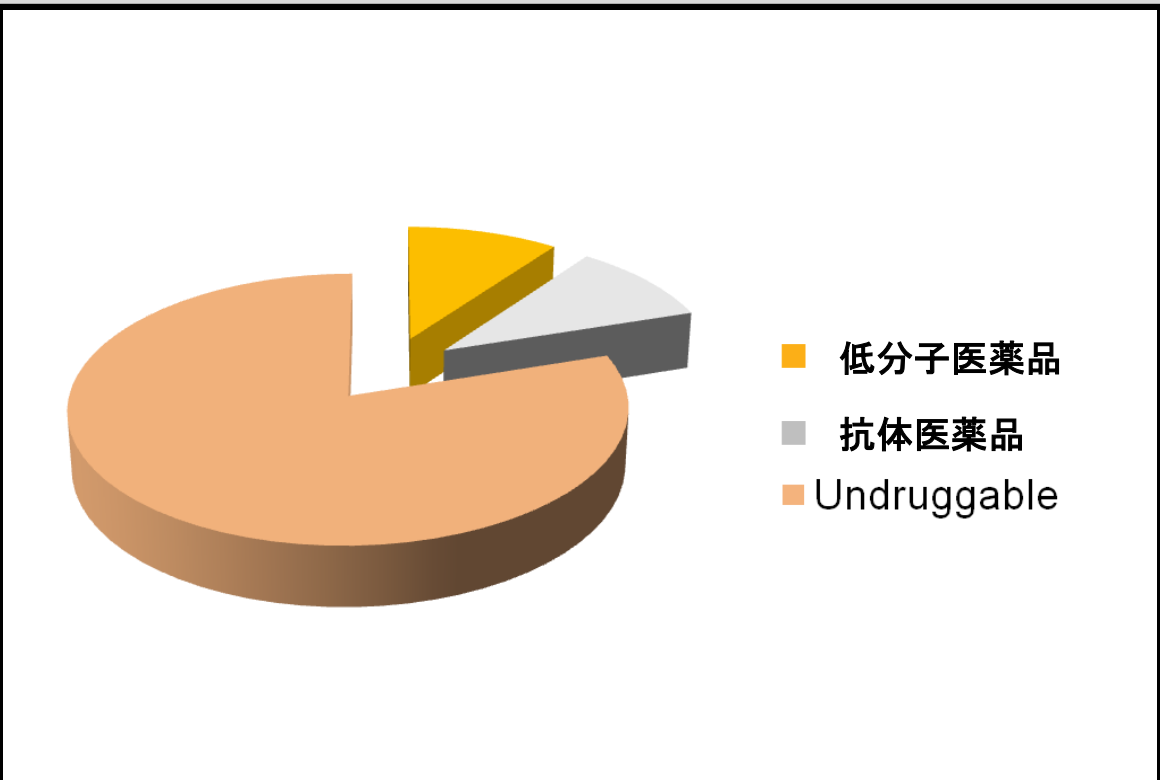
2014年4月29日、スイス・バーゼル発 – ノバルティスは、本日、LDK378がクリゾチニブによる治療後に疾患が進行したかクリゾチニブ不耐容のALK+ NSCLC患者さんの治療薬として、米食品医薬品局（FDA）から承認を取得したと発表しました[1]。LDK378の承認は、前治療が奏効しなくなったALK+ NSCLC患者さんのアンメット・メディカル・ニーズに応えるものです。

治験総括医師を務める米ボストンマサチューセッツ総合病院がんセンターのアリス・ショー医学博士（Alice T. Shaw, MD, PhD, Massachusetts General Hospital Cancer Center, Boston）は次のように述べています。「LDK378は、クリゾチニブによる初回治療開始後に進行したALK+ NSCLCの患者さんにとって重要な治療選択肢を意味します。今回承認されたことで患者さんに新たなALK阻害剤を用いた治療を引き続き提供できるようになり、ALK+ NSCLCのマネジメントとモニタリングに影響を与えることになります」

世界的に、がんによる死亡原因の第一位は肺がんです。肺がんの中でもっとも多く見られるのがNSCLCであり、全肺がん症例の85～90%を占めています[3]。その中の2～7%はALK遺伝子の変異によってがん細胞の成長が促進されるタイプのがんで、この変異の有無は、腫瘍細胞の分子診断によって同定することが可能です[2]。ALK+ NSCLCの患者さんの治療法は大きく前進しているものの、疾患の進行は不可避であることが多く、更なる治療選択肢が望まれています。

低分子医薬品 & 抗体医薬品のジレンマ

それぞれの限界と“Undruggable”標的タンパク群



80% of all existing targets are beyond the reach of the two established classes of drugs[1]

[1] Verdine and Walensky 2007, Clin Cancer Res 13:7264

- タンパク質表面に低分子医薬品が結合可能なポケット（様なところ）が存在しない
- 基本的に抗体医薬品は細胞内のタンパク質を標的にできない
- “Undruggable”とは単に低分子/抗体医薬品では標的にできなかったタンパク質群

General Drug Discovery Process

Target Discovery

How can we identify suitable biological targets ?

How can we understand the underlying mechanism or cause of the disease ?

Does this disease represent a significant unmet medical need in patients ?

Drug Discovery

How can we validate biological targets ?

Does the molecule contribute to target validation ?

Can we identify suitable starting molecule ?

Traditional HTS/Fragment Screening for Hit Finding

Diversity of chemical library is critical

Biological targets

3-12 months for protein production and setting up assay, counter-assays etc

HTS/FBDD

12 months if hits available, for hit validation, biophysical confirmation etc

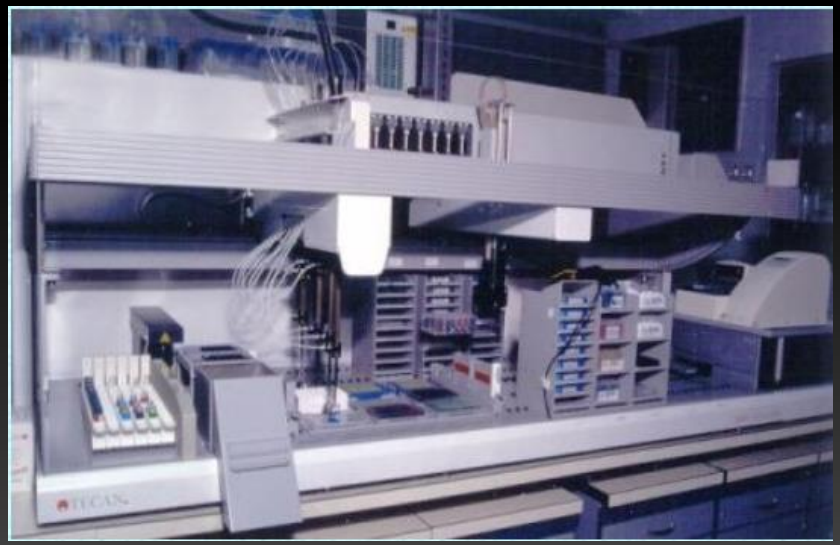
Weak Hits

12-36 months, even more for medchem efforts to gain suitable potency and properties

Optimized Hits

Structural info

Target Validation



New Scheme for Hit Finding

Combined diversity is built up for the requirement of target protein structure

Biological targets

1-2 months for protein production

PDPS (Peptide Discovery Platform System)

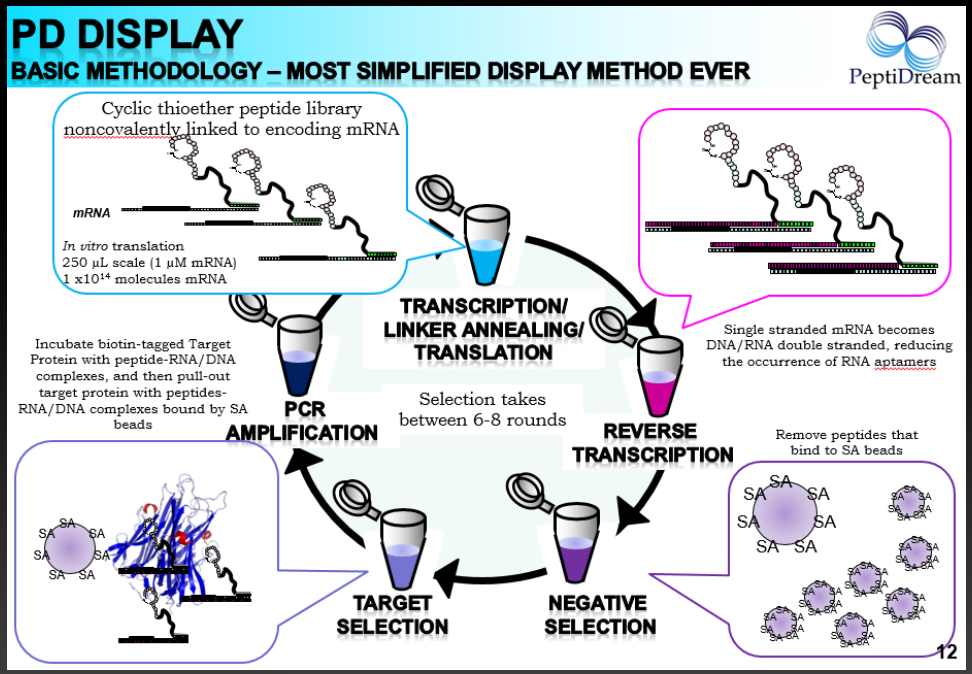
1-4 months for high affinity peptide selection including counter assays

Strong Hits

1 month for chemical synthesis of tool peptide

Structural info

Target Validation



Constrained Peptides: Highlights and Achievements

- Exceptional affinity (best ~50pM pre-optimization) and exceptional selectivity seen for a wide variety of cyclic and helical peptide structures covering a wide variety of molecular diversity.

- More than 150 XRay structures solved to date (against various targets), novel binding modes and epitopes identified. Truly a novel class of therapeutics that is hitting space never before hit. Consider to be one of the best hit-finding platforms available.

- Excellent stability, many with long half-lives (16hrs+), some high protein bound (very tunable), some good tissue penetration, most very low renal clearance, surprisingly good PK/PD(*cMax driven (30-60uM on a 5mg/kg dose) or AUC driven (30-60uM/h on 5mg/kg dose); both applicable*), no toxicity, no organ accumulation, or immunogenicity observed to date in vivo. PK profiles compatible with once a day dosing.

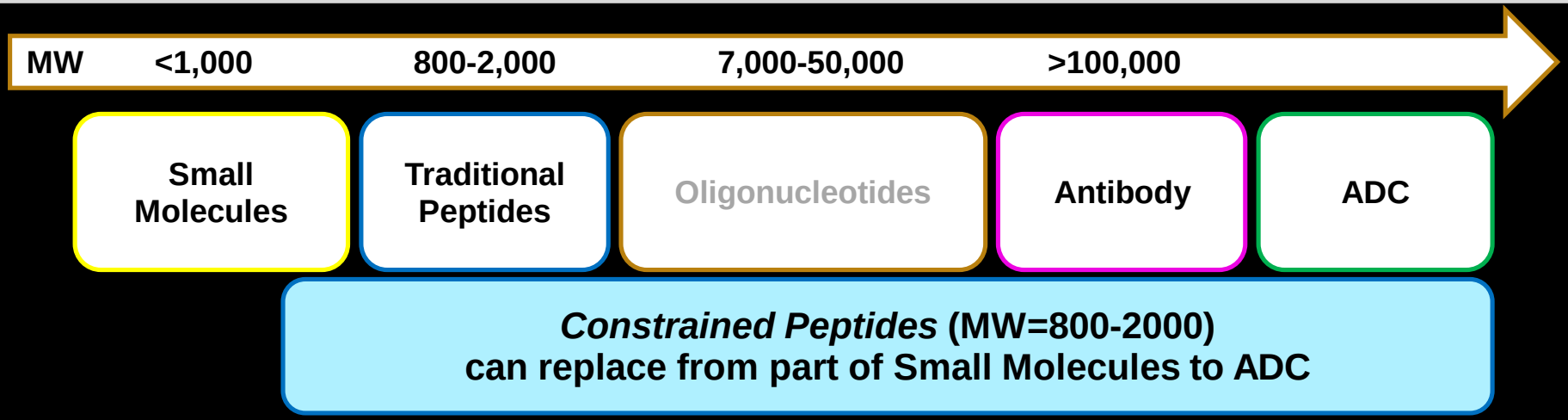
- SC, IV, Oral, and Nasal delivery routes have been explored. Skin (patch) is also possible, but dose load is a current limitation. Depo has not been explored as of yet. Stable through the gut. Intestinal uptake – cyclic 6, 7 & now 8 mers (contain N-Me residues) with excellent bioavailability (best 86% - 920Da) – still expanding the space. Some cell permeable – thioether cyclic (largest is thioether cyclic 15mer thus far) and helical (13-14mer), applying learnings to all collaborations and library design and optimization.

- Technology allows for building SAR, Alanine scanning, N-methyl scanning, and various optimization methods >>speed >> that cannot be done quickly with medchem approaches, thus provides an excellent supplement to medchem approach better done by partners, but doesn't completely eliminate medchem.

- Therapeutic space and application is truly limitless.

Constrained peptides can contribute or replace

Many advantages for other approaches



- ✓ Identify probe peptides quickly (instead of HTS)
- ✓ Enable to help biological validation
- ✓ Give quick decision Go/No-go
- ✓ Identify unexpected binding pockets
- ✓ Supply pharmacophore information (superior than FBDD or de-peptidic)

- ✓ Identify equal or even better affinity peptides easily
- ✓ New avenue of alternatives for antibody
- ✓ Less/No antigenicity
- ✓ Easier preparation
- ✓ Cheaper production
- ✓ Easier QC control (single composition)

- ✓ Potential oral available
- ✓ Highly potential i.v and topical administration
- ✓ Great proteolytic stability
- ✓ Permeability modifiable
- ✓ Less/No antigenicity
- ✓ In vivo activity confirmed in many cases

- ✓ PDC (peptide-drug conjugation) being an alternative
- ✓ Easy to control how many toxin loading
- ✓ Less/No antigenicity
- ✓ Easier preparation
- ✓ Cheaper production
- ✓ Easier QC control (single composition)

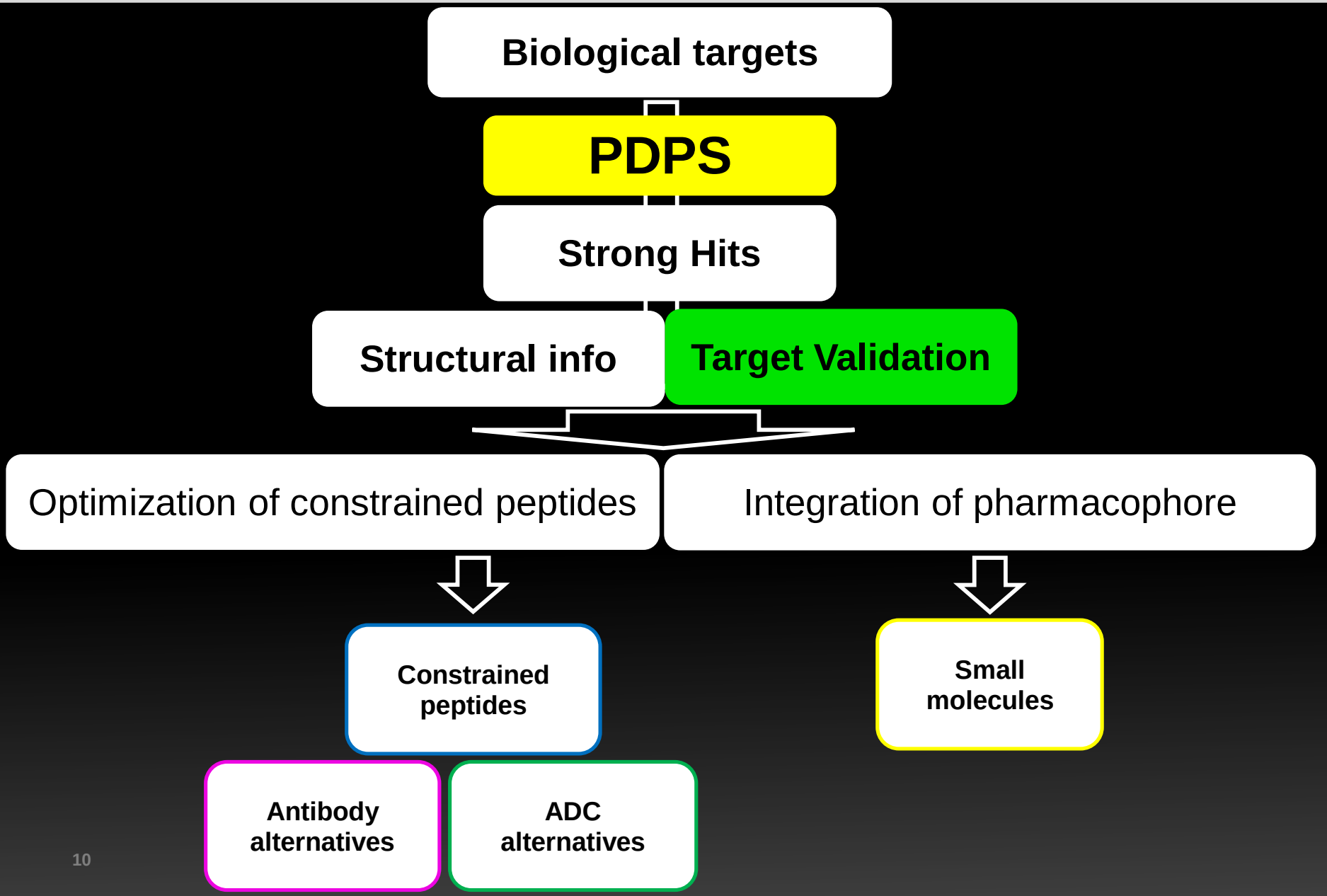
Constrained peptide can replace existing Antibody

Even stronger affinity

PeptiDream Announces Filing of a Patent by Bristol-Myers Squibb for Macrocyclic Peptide Inhibitors of the PD-1/PD-L1 and CD80(B7-1)/PD-L1 Protein/Protein Interaction Identified from Drug Discovery Alliance

TOKYO, JAPAN – October 7th, 2014 – PeptiDream Inc., a public Tokyo-based biopharmaceutical company ("PeptiDream")(Tokyo:4587) announced today the publication of a patent entitled "macrocyclic inhibitors of the PD1/PD-L1 and CD80(B7-1)/PD-L1 Protein/Protein Interactions" by US-based Bristol-Myers Squibb (NYSE:BMY). The patent describes macrocyclic peptides that inhibit the PD-1/PD-L1 and PD-L1/CD80 protein/protein interaction, and thus are useful for the amelioration of various diseases, including cancer and infectious disease. The macrocyclic peptides described in the patent were discovered using PeptiDream's PDPS technology in collaboration with Bristol-Myers Squibb. PD-L1 is expressed on tumor cells and its upregulation helps cancers evade the host immune system. Inhibiting the PD-L1/PD-1 interaction has been shown to effectively increase the body's natural ability to fight tumors. At current, the PD-1/PD-L1 interaction is considered to be the hottest target in the immune-oncology field, with potential sales of tens of billions of dollars per year expected. There is a variety of antibody therapeutics targeting this interaction in clinical trials, with Bristol-Myers Squibb already receiving marketing approval in Japan for Nivolumab, an antibody targeting PD-1. AstraZeneca, Merck, Roche, and several other companies also have antibodies in late stage trials. There are no reported peptide or small molecule inhibitors against PD-1/PD-L1. PeptiDream's CSO Patrick C. Reid was listed as one of the inventors.

New Grammar for Drug Discovery



Summary

- PeptiDream's PDPS can offer new grammar of drug discovery
- Evolution of "Peptide drugs" is now going on
- PDPS has a big synergistic impact for small molecule drug discovery
- Antibody can be replaced by constrained peptides
- ADC can be also replaced by PDC with constrained peptides