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Genomics drugs in clinical trials

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Ten years ago, a first draft of the sequence of the human genome was announced, amid promises of better drugs to come through improved understanding of disease, as highlighted by Kramer and Cohen (*Nature Rev. Drug Discov.* **3**, 965–972; 2004)[1]. However, the tone of some recent commentaries reflects disappointment with the perceived outcome[2,3]. We believe that an objective discussion of this important topic has been hampered by both a lack of clarity about what constitutes a genomics drug and a lack of visibility of important genomics contributions to drug discovery. For example, recent articles have highlighted belimumab, a monoclonal antibody (mAb) that targets B lymphocyte stimulator (BLYS; also known as TNFSF13B/BAFF), as having life-altering potential for patients with systemic lupus erythematosus (SLE)[4], but have failed to mention its clear-cut genomics origins.

We therefore searched the clinical pipelines of several genomics companies using the Thomson Reuters Integrity database and literature resources for drugs in which genomics data — for example, from sequencing, database mining, expression profiling or RNA-interference screening — seems to have had an essential role; that is, in the absence of the genomics data, a project would probably not have been initiated or progressed. As the drug development timeline is typically 10–15 years, we limited the search to drugs that are in Phase II or III trials. Here, we highlight 12 drugs that illustrate the wide-ranging impact of essential genomics data to drug discovery (TABLE 1). Subjective judgment was often needed during the selection, especially in cases in which pre-existing literature linked a target to the disease prior to genomics experiments.

High-throughput sequencing of cDNA libraries was the first genomics technology. It produced partial sequences of expressed genes (expressed sequence tags; ESTs) that could be assembled and mined by bioinformaticians for genes that had specific expression in disease tissues. Several private and public organizations began populating databases with ESTs as a prelude to the full sequencing of the human genome, and these served as a rich source of novel drug targets. Thus, sequencing of a neutrophil monocyte-derived cDNA library led to the discovery of BLYS, a member of the tumour necrosis factor (TNF) family that induces B cell proliferation[5,6]. High levels of circulating BLYS are found in patients with SLE, and transgenic mice expressing BLYS develop a lupus-like disease. As mentioned above, the BLYS-specific mAb belimumab antagonizes the function of BLYS. Phase I and II trials of belimumab showed promising results[7,8], and in two Phase III trials the primary end point was reportedly met in a large proportion of patients with SLE receiving high-dose belimumab[4]. These data provided the basis for its recent regulatory submission. The identification of BLYS by genomics prompted the search for its receptors[9] and led indirectly to the development of atacicept, a soluble BLYS receptor that has also been tested in patients with SLE[10].

During a race to identify new members of the TNF receptor family by database mining of ESTs, TNF-related apoptosis-inducing ligand (TRAIL) receptor 1 (TRAIL-R1; also known as DR4/TNFRSF10A)[11] and TRAIL-R2 (also known as DR5/TNFRSF10B)[12] were discovered. Binding of the ligand TRAIL activates these receptors and initiates the apoptosis cascade in tumour cell lines. Therefore, the disruption of the ligand–receptor interaction was of potential utility in the treatment of some cancers. TRAIL itself was identified by mining the EST database from the National Center for Biotechnology Information (NCBI)[13] and led to the development of a recombinant protein therapeutic, dulanermin, which is currently in clinical trials for various cancers.

Mapatumumab is an agonistic human mAb that binds to TRAIL-R1 and induces apoptosis in cancer cells. It was among the first of several TRAIL receptor-specific mAbs to enter the clinic and has been tested in Phase I and II trials as a single agent and also in combination studies[14]. Apomab is a mAb agonist of TRAIL-R2 that is also in cancer clinical trials[15]. Thus, database mining of genome-wide cDNA sequence libraries led to the discovery of TRAIL, TRAIL-R1 and

Table 1 | **Selected genomics drugs in clinical development**

Drug	Drug target	Associated genomics company during discovery phase	Indication*	Phase*
Belimumab	BLYS	Human Genome Sciences	Systemic lupus erythematosus	Preregistration
Atacicept	BLYS receptor	ZymoGenetics	Systemic lupus erythematosus	II/III
Mapatumumab	TRAIL-R1	Human Genome Sciences	Cancer	II
Apomab	TRAIL-R2	Genentech	Cancer	II
Dulanermin	TRAIL	Amgen/Genentech	Cancer	II
Odanacatib	Cathepsin K	Celera	Postmenopausal osteoporosis	III
AMG-785	Sclerostin	Amgen	Postmenopausal osteoporosis	II
DG-041	Prostanoid EP_3 receptor (antagonist)	deCODE Genetics	Peripheral arterial obstructive disease	II
OC-000459	CRTH2 receptor (antagonist)	Oxagen	Asthma	II
PLX-4032	BRAF kinase	Plexxikon	Metastatic melanoma	III
LX-1031	TPH1	Lexicon Pharmaceuticals	Irritable bowel syndrome	II
LX-1032	TPH1	Lexicon Pharmaceuticals	Carcinoid syndrome	II

BLYS, B lymphocyte stimulator (also known as TNFSF13B/BAFF); TPH1, tryptophan hydroxylase 1; TRAIL-R1, TNF-related apoptosis inducing ligand (TRAIL) receptor 1 (also known as DR4/TNFRSF10A); TRAIL-R2, also known as DR5/TNFRSF10B. *Data extracted from Thomson Reuters Integrity database on 28 September 2010.

TRAIL-R2, and established these as targets for the development of biologics as genomics drugs for the treatment of cancer.

Cathepsin K is a cysteine protease that was identified in cDNA libraries derived from bone cells[16]. Its high, selective expression in osteoclasts implicated the protease in bone remodelling processes and genetics data (mutations in cathepsin K cause pycnodystosis) suggested that its inhibition might decrease pathological bone resorption in osteoporosis. Several cathepsin K inhibitors have entered clinical trials, but development has been difficult. However, a dose-finding study in postmenopausal women with low bone density showed that treatment with the cathepsin K inhibitor odanacatib increased bone mineral density in lumbar spine and in the hip[17], and a Phase III trial is ongoing.

Access to the complete sequence of the human genome has revolutionized genetic studies by providing new markers and rapid gene-mapping methods. One of the most significant recent discoveries in bone disorders emerged from genetic studies in patients with sclerosteosis. A genome-wide linkage analysis in 22 affected families of the Afrikaneer population unveiled loss-of-function mutations in the *SOST* gene, which encodes sclerostin, a protein that is secreted by osteoblasts and negatively regulates bone formation[18]. The mutations cause severe bone overgrowth, suggesting that pharmacological inhibition of sclerostin may increase bone density. AMG-785, a mAb that targets sclerostin, has been tested in Phase I trials[19] and is currently in Phase II trials for the treatment of osteoporosis.

At deCODE Genetics, genome-wide linkage scans have been conducted in Icelandic patients suffering from atherosclerosis. In one scan, a search for genes linked to peripheral arterial obstructive disease implicated the *PTGER3* gene, which encodes the EP_3 prostaglandin receptor[20]. A medicinal chemistry effort yielded a potent EP_3 receptor antagonist, DG-041, which has progressed to Phase II clinical trials.

In a strategy intended to ensure the druggability of targets discovered using genetics, scientists from Oxagen restricted genotyping of patients to the family of G protein-coupled receptors (GPCRs)[21], all members of which have now been identified in the human genome. During a genome-wide association study, the *CRTH2* gene was found in a linkage region for asthma. *CRTH2* encodes a GPCR for the prostaglandin PGD_2, which had previously been linked to inflammatory diseases. A medicinal chemistry programme produced OC-000459, a CRTH2 antagonist, which has progressed to Phase II trials for the treatment of respiratory and gastrointestinal inflammatory disorders.

As part of an early genome-wide search for cancer genes focusing on mutations in the RAS–MAP kinase pathway, the sequencing of cancer patient cell lines through the coding exons of BRAF kinase revealed several gain-of-function mutations[22]. High-throughput sequencing in hundreds of primary human cancer cell lines then confirmed BRAF as an important oncogene in malignant melanoma. A potent selective inhibitor of a BRAF mutant (PLX-4032) was subsequently developed at Plexxikon[23]. Positive Phase I trial data with PLX-4032 prompted an extension trial in patients expressing the BRAF mutation, a large proportion of whom experienced tumour regression[24]. Phase II and III studies of PLX-4032 are ongoing.

Access to the complete sequences of human and mouse genomes has greatly advanced the use of mouse knockout technology in drug discovery. During a programme to study phenotypes of 5,000 gene knockouts, a new brain-specific isoform of tryptophan hydroxylase (TPH) was discovered[25]. Dysregulation of TPH in the gastrointestinal tract is associated with carcinoid syndrome, as well as with irritable bowel syndrome (IBS), and so the discovery of tissue-specific TPH isoforms prompted the search for serotonin inhibitors devoid of central nervous system-derived side effects. Two TPH inhibitors, LX-1031 and LX-1032, subsequently entered Phase II trials for the treatment of IBS (LX-1031) and carcinoid syndrome (LX-1032).

In summary, we have selected 12 drugs that, in our view, would probably not exist had it not been for genomics data. We argue that these drugs should be seen as the tip of the iceberg because this limited analysis only captured drugs originating from genomics companies and whose histories are documented in the literature. We conclude that the first decade of the genomics era has provided new, possibly valuable drug targets for some important diseases. Although genomics technologies are not substitutes for hypothesis-driven disease biology, medicinal chemistry and clinical testing, they have become firmly embedded in the drug discovery process and it seems likely that many more drugs in the foreseeable future will be genomics drugs.

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1. Kramer, R. & Cohen, D. Functional genomics to new drug targets. *Nature Rev. Drug Discov.* **3**, 965–972 (2004) .
2. Editorial. The human genome at ten. *Nature* **464**, 649–650 (2010).
3. Garnier, J.-P. Rebuilding the R&D engine in big pharma. *Harv. Bus. Rev.* **86**, 68–76 (2008).
4. Dall'Era, M. & Wofsy, D. Connective tissue diseases: belimumab for systemic lupus erythematosus: breaking through? *Nature Rev. Rheumatol.* **6**, 124–125 (2010).
5. Moore, P. A. *et al.* BLyS: member of the tumor necrosis factor family and B lymphocyte stimulator. *Science* **285**, 260–263 (1999)
6. Mackay, F., Schneider, P., Rennert, P. & Browning, J. BAFF and APRIL: a tutorial on B cell survival. *Annu. Rev. Immunol.* **21**, 231–264 (2003).
7. Furie, R. *et al.* Biologic activity and safety of belimumab, a neutralizing anti-B-lymphocyte stimulator (BLyS) monoclonal antibody: a phase I trial in patients with systemic lupus erythematosus. *Arthritis Res. Ther.* **10**, R109 (2008).
8. Wallace, D. J. *et al.* A phase II, randomized, double-blind, placebo-controlled, dose-ranging study of belimumab in patients with active systemic lupus erythematosus. *Arthritis Care Res.* **61**, 1168–1178 (2009).
9. Gross, J. A. *et al.* TACI and BCMA are receptors for a TNF homologue implicated in B-cell autoimmune disease. *Nature* **404**, 995–999 (2000).
10. Nestorov, I., Papasouliotis, O., Pena Rossi, C. & Munafo, A. Pharmacokinetics and immunoglobulin response of subcutaneous and intravenous atacicept in patients with systemic lupus erythematosus. *J. Pharm. Sci.* **99**, 524–538 (2010).
11. Pan, G. *et al.* The receptor for the cytotoxic ligand TRAIL. *Science* **276**, 111–113 (1997).
12. Sheridan, J. P. *et al.* Control of TRAIL-induced apoptosis by a family of signaling and decoy receptors. *Science* **277**, 818–821 (1997).
13. Wiley, S. R. *et al.* Identification and characterization of a new member of the TNF family that induces apoptosis. *Immunity* **3**, 673–682 (1995).
14. Moretto, P. & Hotte, S. J. Targeting apoptosis: preclinical and early clinical experience with mapatumumab, an agonist monoclonal antibody targeting TRAIL-R1. *Expert Opin. Investig. Drugs* **18**, 311–325 (2009).
15. Fox, N. E., Humphreys, R., Luster, T. A., Klein, J. & Gallant, G. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptor-1 and receptor-2 agonists for cancer therapy. *Expert Opin. Biol. Ther.* **10**, 1–18 (2010).
16. Kometani, M., Kazuhiko, N., Tomoo, T. & Niwa, S. Hurdles in the drug discovery of cathepsin K inhibitors. *Curr. Top. Med. Chem.* **10**, 733–744 (2010).
17. Bone, H. G. *et al.* Odanacatib, a cathepsin-K inhibitor for osteoporosis: a two-year study in postmenopausal women with low bone density. *J. Bone Miner. Res.* **25**, 937–947 (2010).
18. Brunkow, M. E. et al. Bone dysplasia sclerosteosis results from loss of the *SOST* gene product, a novel cystine knot-containing protein. *Am. J. Hum. Genet.* **68**, 577–589 (2001).
19. Padhi, D., Jang, G., Stouch, B., Fang, L. & Posvar, E. Single-dose, placebo-controlled, randomized study of AMG 785, a sclerostin monoclonal antibody. *J. Bone Miner. Res.* 30 Jun 2010 (doi:10.1002/jbmr.173).
20. Gudmundsson, G. *et al.* Localization of a gene for peripheral arterial occlusive disease to chromosome 1p31. *Am. J. Hum. Genet.* **70**, 586–592 (2002).
21. Pettipher, R., Mangion, J., Hunter, M. G. & Mackay, I. Identification of G-protein-coupled receptors involved in inflammatory disease by genetic association studies. *Curr. Opin. Pharmacol.* **5**, 412–417 (2005).
22. Davies, H. *et al.* Mutations of the *BRAF* gene in human cancer. *Nature* **417**, 949–954 (2002).
23. Bollag, G. *et al.* Clinical efficacy of a RAF inhibitor needs broad target blockade in BRAF-mutant melanoma. *Nature* **467**, 596–599 (2010).
24. Flaherty, K. T. *et al.* Inhibition of mutated, activated BRAF in metastatic melanoma. *N. Engl. J. Med.* **363**, 809–819 (2010).
25. Yu, X., Miranda, M. & Hu, Y. Protein and cDNA sequence of human tryptophan hydroxylase homologs. WO2002097039 (2002).

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