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A chemogenomic approach to drug discovery: focus on cardiovascular diseases

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References to individual protein targets and bioactive small molecules associated with cardiovascular diseases can be found in multiple bibliographic sources. From mining these sources, a highly curated list of 214 cardiovascular targets was collected and organised using functional classification schemes for the main protein families of therapeutic relevance, namely, enzymes, G-protein-coupled receptors, ion channels, and nuclear receptors. This list was then used to interrogate annotated chemical libraries and extract a chemical space of 44 032 small molecules connected to 160 targets. Some of these bioactive ligands were also found to have affinity for an additional set of 421 proteins not linked originally to cardiovascular diseases, thus constituting a valuable indirect source to complete the cardiovascular target space and infer a potential off-cardiovascular target space.

Introduction

Cardiovascular diseases continue to be the main cause of death in developed countries. In the United States, they account for approximately 40% of total mortality, with over 70 million people being estimated to be suffering from some type of cardiovascular problem [1]. The picture is similar in Japan and the countries of the European Union. Since many cardiovascular events are not necessarily fatal, but interfere with the ability of the individual to lead a normal daily life, the associated healthcare costs are enormous. Consequently, devising novel strategies for the generation of safer drugs devoid of cardiovascular risks, but also more efficient to prevent and treat cardiovascular diseases, is of great significance to public health [2,3].

Traditionally, cardiovascular drug discovery has been based on a process generally referred to as 'forward pharmacology' [4]. Within this paradigm, target identification is the result of an initial observation of some biological activity associated with a specific biological sample. This is followed by the characterisation of the chemical entity responsible for such biological activity, which is subsequently utilised to uncover the particular target responsible for its pharmacodynamic action. Recent progress in genomics and proteomics, alongside technological advances in high-throughput chemical synthesis and biological screening, are opening an avenue toward more systematic, information-rich approaches to cardiovascular research [5,6]. Within this scenario, the conventional process can be reversed by identifying putative novel cardiovascular targets first, then developing screening assays to identify new chemical entities that, after careful optimisation of their physicochemical and pharmacological properties, may provide ultimate confirmation for the physiological significance of the original target proposals [7].

Either by forward or reverse pharmacology, numerous protein targets with proven association with cardiovascular events have been identified over the years. In parallel, medicinal chemistry programs have delivered thousands of small molecules with confirmed bioactivity for many of those cardiovascular targets. This vast amount of information on ligands and targets relevant to cardiovascular diseases is eventually published in the scientific literature, though scattered over many hundreds of original and review articles. The aim of this work is to compile, classify, and integrate existing prior knowledge on cardiovascular targets and ligands and by doing so to provide a comprehensive perspective of the currently explored pharmacological space relevant to cardiovascular drug discovery.

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Cardiovascular target space

The compilation of a comprehensive list of biological targets with validated association with cardiovascular events suffers from some of the difficulties inherent to the process of information retrieval and entity recognition [8]. In spite of the existence of official target names recommended by nomenclature committees for enzymes [9] and receptors [10], alternative names are still widely utilised in scientific publications. For example, the use of the term angiotensin-converting enzyme or its acronym (ACE) is generalised, even though peptidyl-dipeptidase A is the recommended name for that enzyme (EC 3.4.15.1). Many biomedical information-retrieval services (such as PubMed) make use of internal thesauri to expand automatically the query with other related entity terms. Unfortunately, this is not sufficient in many instances and important information is not recovered unless searches considering all official and alternative disease and protein terms are made. Accordingly, a more traditional strategy was adopted, consisting initially of identifying all publications in PubMed containing the co-occurrence of disease-related generic terms (such as 'cardiovascular', 'thrombosis', 'dyslipidemia', 'ischemia') with protein-related generic terms (such as 'protein', 'enzyme', 'receptor', 'channel'), followed by the actual reading of all abstracts and body texts, whenever necessary. The process of entity recognition was performed with the help of an annotated protein thesaurus composed of over 30 000 protein and protein family name synonyms and abbreviations. This rather time-consuming manual approach identified 1065 review and original primary articles from 129 scientific journals covering the 20-year period spanning 1988 and 2007 and mapping well-defined cardiovascular terms to 214 specific protein entities (see Supplementary material). It is important to acknowledge at this stage that this set of 214 proteins positively associated with cardiovascular events is, most probably, far from being complete but, because of the nature of the strategy followed, it certainly constitutes a highly curated collection of representative cardiovascular targets.

This first list of 214 proteins linked to cardiovascular diseases with confirmed bibliographical evidence contained validated targets that may be able to prevent or treat cardiovascular events, as well as targets associated with cardiovascular risks [2]. As representatives of the former, thrombin and factor Xa are key enzymes in the coagulation cascade, and thus, they have been classic cardiovascular targets in the search for orally active anticoagulants [11]. By contrast, the serotonin 5-HT_{2B} receptor is an illustrative example of the latter, as agonism at this receptor has been recently linked to cardiac valvulopathy [12]. Organising these 214 targets into the main protein families of therapeutic relevance revealed that the currently explored cardiovascular target space is composed of 144 enzymes, 38 G-protein-coupled receptors (GPCRs), 21 ligand-gated ion channels, and 11 nuclear receptors (Figure 1). This organisation highlights the importance of enzyme targets for cardiovascular drug discovery, although one may argue that their over-representation in the current cardiovascular target space may have been historically biased by some target tractability and druggability aspects intrinsically associated with this protein family. Among the list of enzymes, 40 targets are oxidoreductases, 50 are transferases (including 33 kinases), 48 are hydrolases (including 26 proteases), 5 are lyases, and 1 is an isomerase; for GPCRs, however, almost half of the targets belong to the class A rhodopsin-like biogenic amine family. The organisation of cardiovascular targets in protein families constitutes an important aspect in cardiovascular chemogenomics [13].

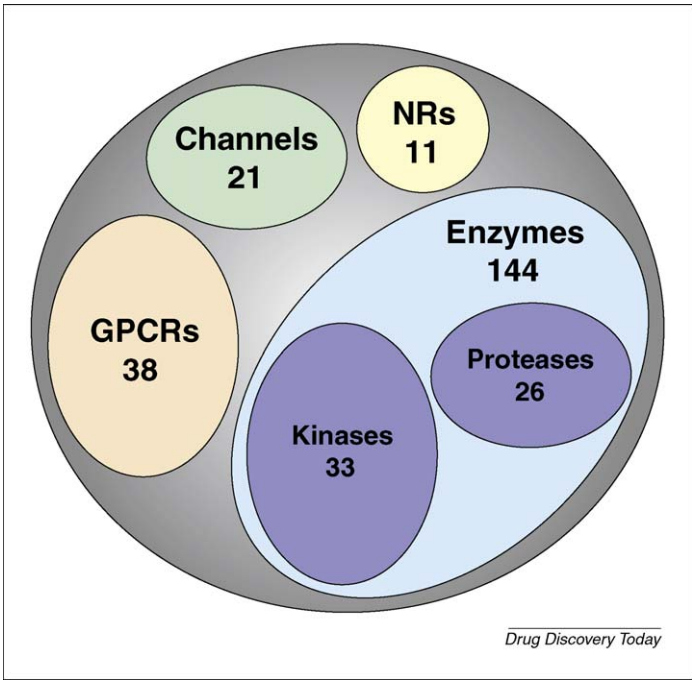

FIGURE 1

Distribution of the 214 proteins linked to cardiovascular events among the four main protein families of therapeutic relevance, namely, enzymes (with particular focus on kinases and proteases), G-protein-coupled receptors (GPCRs), ion channels, and nuclear receptors (NRs).

Structural coverage of cardiovascular targets

The next step requires the establishment of the knowledge base of the cardiovascular target space defined. An important aspect involves assessing the degree of structural coverage within protein families as a means of determining the level of applicability of structure-based methods for *in silico* target profiling [14]. A web resource called Functional Coverage of the Proteome (FCP) [15] was used for this purpose; it organises the contents of the Protein Data Bank (PDB) [16] using standard classification schemes for protein families, namely, enzymes (with separate classifications for kinases and proteases), GPCRs, ion channels/transporters, and nuclear receptors.

Of the 214 targets associated with cardiovascular diseases, representative structures were identified in the PDB for 62.6% of them (Figure 2a). Of the 134 targets with experimentally determined structure, 113 were enzymes (including 21 kinases and 25 proteases), 11 were nuclear receptors, 8 were ion channels, and 2 were GPCRs, which would imply that 78.5%, 100%, 38.1%, and 5.3% of the respective cardiovascular-relevant targets within each protein superfamily have at least one representative structure in the PDB. Constraining the analysis to the availability of structures for *Homo sapiens*, the number of structurally covered targets is just over 50% of all cardiovascular-relevant targets and includes 92 enzymes, 10 nuclear receptors, 5 ion channels, and 2 GPCRs. The structural coverage of those targets is not, however, uniformly distributed and while 3 targets contain more than 200 structures

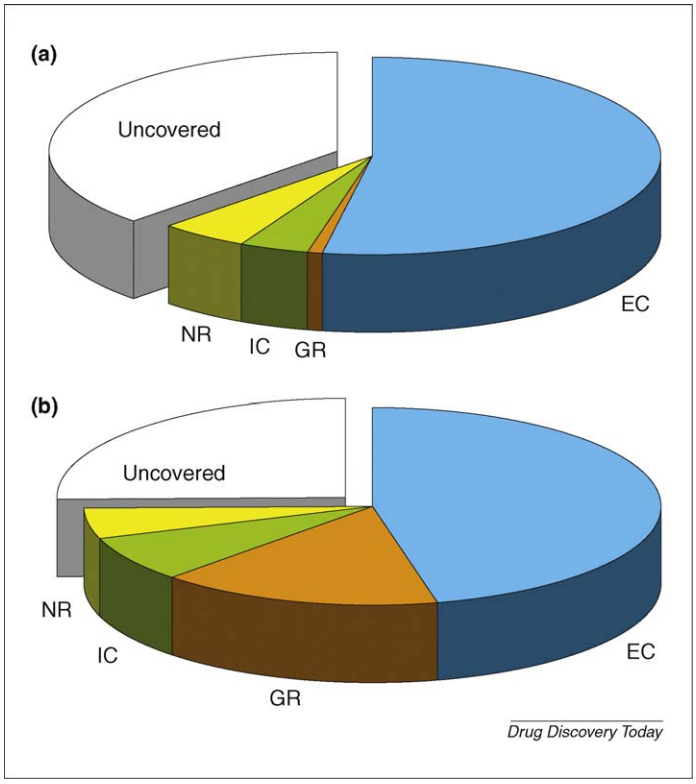

FIGURE 2

Structural and chemical coverage in cardiovascular target space. (a) Distribution of targets for which at least one representative structure exists in the Protein Data Bank and (b) distribution of targets for which at least one bioactive ligand is present in the annotated chemical libraries considered. EC: enzymes; GR: GPCRs; IC: ion channels; NR: nuclear receptors.

(namely, carbonate dehydratase, thrombin, and protein tyrosine phosphatase), 55 targets are represented by fewer than 5 structures.

Overall, structural coverage analysis reveals that *in silico* cardiovascular profiling, based on protein structures obtained experimentally by X-ray crystallography, is currently feasible for the majority of disease-relevant targets. In order to approach completeness, however, the construction of comparative structural models by computational means would still be necessary for the remaining 37.4% of the 214 cardiovascular targets identified, with all the implications that the use of modeled conformations may have on the performance of docking calculations [17]. In this respect, the recent determination of the first two human GPCR structures for the adrenergic β2 [18] and adenosine 2A receptors [19] paves the way to expanding significantly in the near future the structural coverage within this family of utmost therapeutic relevance.

Cardiovascular pharmacological space

In the past few years, considerable efforts have been invested into constructing chemical libraries that incorporate literature-based pharmacological data into traditional molecular repositories [20]. The development of these annotated chemical libraries involves, in many instances, tedious reading of a large number of bibliographic sources, followed by manual drawing of chemical structures and finally, storage with binding or functional data to precisely annotated protein entities. In spite of these technical difficulties, an ample offer of both commercial and public annotated chemical libraries is currently available, which in combination provide an invaluable means for estimating the chemical space explored historically around protein targets that can in turn be exploited to develop ligand-based methods for *in silico* target profiling [14].

In this analysis, a representative sample of the available annotated chemical libraries was used. It included WOMBAT [21], a commercial collection of small molecules with known biological activity from medicinal chemistry literature, BindingDB [22], a publicly accessible database of experimentally determined binding affinities of protein–ligand complexes, DrugBank [23], a public resource of drug–target interaction data, and PDSP, a database of experimental K_i data on receptors available from the Psychoactive Drug Screening Program [24].

Chemical coverage of cardiovascular targets

Using the list of 214 cardiovascular targets to interrogate the four repositories of ligand–target interaction data considered, a total of 44 032 unique ligands reported with pharmacological potency of one micromolar or better (pKi, pIC_{50}, or $pEC_{50} \geq 6$) at one or more of those targets were retrieved. Overall, this set of bioactive ligands covered 74.8% of the original cardiovascular target space (Figure 2b). Of these 160 targets that could be interrogated chemically, 99 were enzymes (including 21 kinases and 22 proteases), 34 were GPCRs, 16 were ion channels, and 11 were nuclear receptors, implying that 68.8%, 89.5%, 76.2%, and 100% of the respective cardiovascular targets within each protein superfamily have information on at least one bioactive ligand in the annotated chemical libraries considered. As emphasised above for the structural coverage, however, the chemical coverage of the various targets is not uniformly distributed and while 19 targets are represented by more than 1000 bioactive ligands, 59 targets are connected to fewer than 50 bioactive ligands.

A comparison of the results obtained from the structural and chemical coverage analyses of cardiovascular targets emphasises the fact that the GPCR family is by far the one showing the largest gap between chemical (89.5%) and structural (5.3%) coverage, in contrast to the full structural and chemical coverage attained for all nuclear receptors. Even though, as mentioned above, this situation is likely to improve significantly in the coming years, this means that ligand-based approaches to *in silico* target profiling [25] will continue to occupy an important position in cardiovascular drug discovery.

An analysis of the main structural features present in the small molecules defining this cardiovascular chemical space identified 14 734 atomic frameworks or scaffolds [26]. The frequency of occurrence of those scaffolds among the 44 032 ligands bioactive at cardiovascular targets varies significantly, with only 51 scaffolds representing more than 50 ligands and 9653 scaffolds being exemplified by a single molecule. Figure 3 illustrates the existing relationship between the molecular weight of scaffolds and their associated promiscuity over cardiovascular targets. In agreement with previous reports [27,28], an inverse trend between size and promiscuity is observed, and thus, chemical spaces defined around small scaffolds tend to be pharmacologically richer than those around large more-complex scaffolds.

The structures and protein-family profiles of the five most promiscuous scaffolds within cardiovascular target space are also included in Figure 3. Following early observations [26], a phenyl ring (**1**) is both the most populated and the most promiscuous cardiovascular scaffold. Bioactive molecules being represented by a phenyl

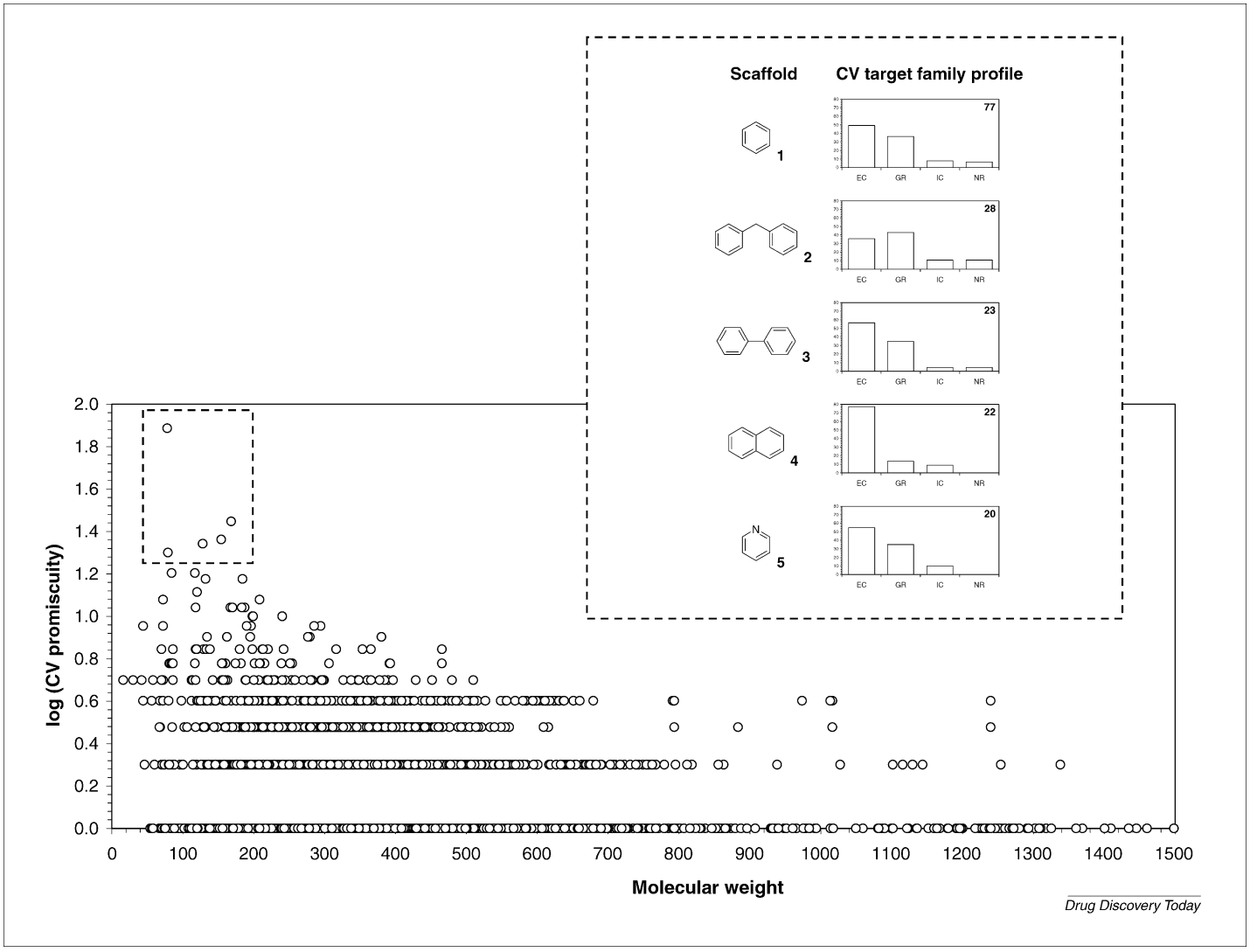

FIGURE 3

Relationship between the molecular weight of the 14 734 scaffolds and their associated cardiovascular promiscuity (in logarithmic units). Also included in the inset are the structures of the five most promiscuous scaffolds together with their corresponding distributions among the main protein families. The target promiscuity of each scaffold is also indicated within each one of the distributions. EC: enzymes; GR: G-protein-coupled receptors; IC: ion channels; NR: nuclear receptors.

scaffold (**1**) are found to be connected to 77 cardiovascular targets, comprising 38 enzymes, 28 GPCRs, 6 ion channels, and 5 nuclear receptors. Also, in accordance with previous findings [29,30], diphenylmethane (**2**) and biphenyl (**3**) are the second and third most promiscuous cardiovascular scaffolds, respectively. Bioactive molecules containing the diphenylmethane scaffold (**2**) possess affinity for 28 cardiovascular targets, including 10 enzymes, 12 GPCRs, 3 ion channels, and 3 nuclear receptors. In turn, bioactive molecules defined by the biphenyl scaffold (**3**) have activity for 23 cardiovascular targets, namely, 13 enzymes, 8 GPCRs, 1 ion channel, and 1 nuclear receptor. Interestingly, the naphthyl ring system (**4**) appears as the fourth most promiscuous scaffold and its bioactive molecules are found to be active across 22 cardiovascular targets, with a clear preference for enzymes (proteases, in particular). Finally, the fifth most promiscuous scaffold is the pyridine ring (**5**), whose span of bioactivity covers a panel of 20 cardiovascular targets. Remarkably, the cumulative promiscuity of these five rather simple scaffolds, all well-known frequently occurring scaffolds in drugs [26], covers 84 of the 214 cardiovascular targets.

Cross-pharmacology of cardiovascular targets

The interaction links established between the set of 44 032 small molecules with reported biological activity to 160 cardiovascular targets offer a means of exploring the existence of potential associations between pairs of targets that may arise as a result of having common bioactive ligands, a property often referred to as cross-pharmacology [31,32]. By connecting target pairs sharing at least one bioactive ligand, a total of 372 cross-pharmacology relationships between 119 cardiovascular targets were retrieved. In particular, the pair of cardiovascular targets composed by the adenosine 1 and 2A receptors is, with 968, the one sharing the largest number of bioactive ligands, followed by the pair formed by the delta and kappa opioid receptors, with 880 common bioactive ligands. The number of common bioactive ligands varies significantly among those 372 target pairs and while 269 target pairs have fewer than 10 shared bioactive ligands, 35 target pairs share over 100 bioactive ligands. Among the latter, 27 pairs are composed of GPCR targets, of which 18 are aminergic GPCRs and the remaining 8 pairs are formed by proteases (6) and nuclear receptors (2).

A more detailed inspection of the identified 372 cross-pharmacology relationships revealed that some targets appear more frequently than others. For example, while the dopamine D_2 receptor had links to 26 different cardiovascular targets, aldehyde reductase showed only one connection. An analysis of these results, from a protein family perspective, revealed that GPCRs showed markedly the highest degree of cross-pharmacology, with every GPCR being connected on average to 11 other cardiovascular targets. Among them, aminergic GPCRs had, on average, 16 connections, whereas peptidic GPCRs were involved, on average, in 6 cross-pharmacology relationships. By contrast, cardiovascular-relevant enzymes were found to be linked to four other targets, on average. Kinases distinguish themselves among enzymes by having, on average, seven connections to other cardiovascular targets. Finally, ion channels and nuclear receptors involved in cardiovascular diseases showed, on average, seven and three links to other targets, respec-

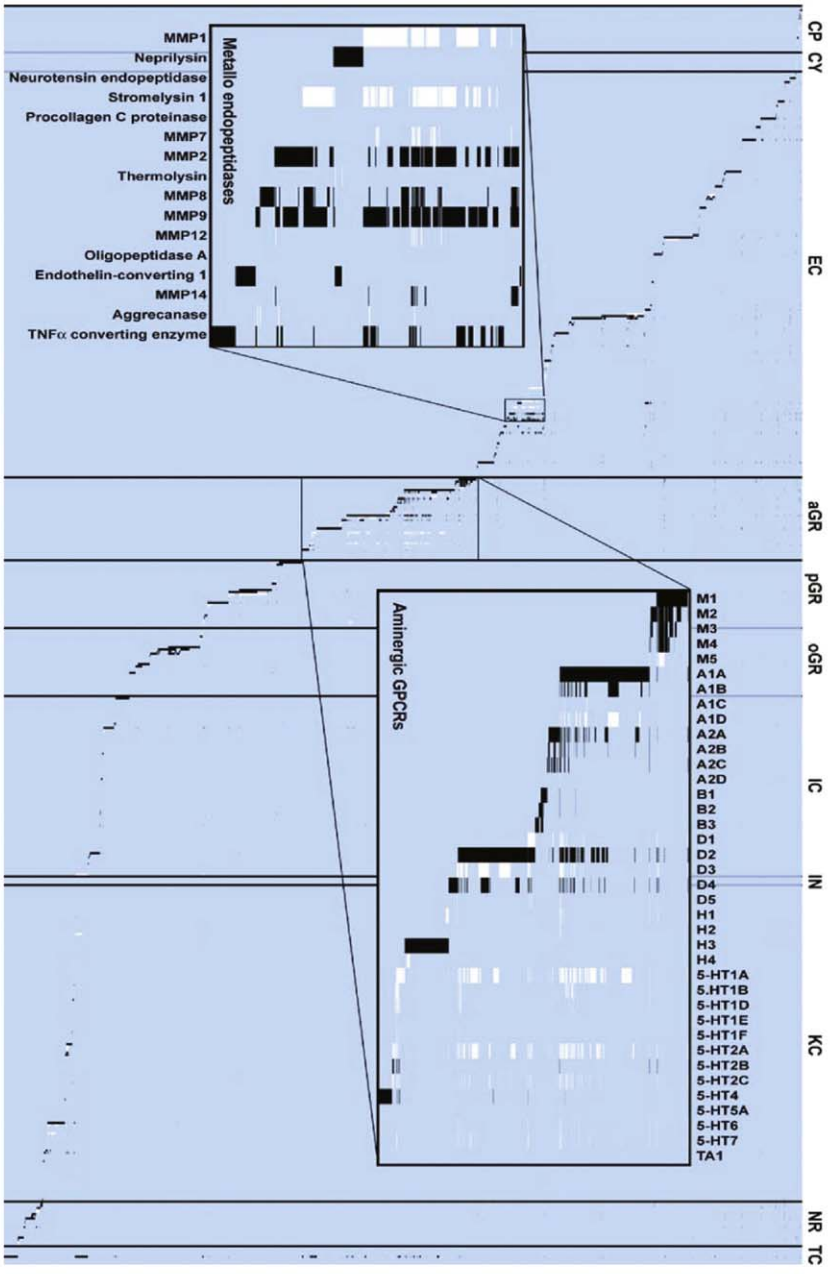

FIGURE 4

Ligand–protein interaction map between the 14 734 scaffolds from all molecules annotated to cardiovascular targets (in columns) and the 581 cardiovascular-relevant proteins (in rows), including the 160 cardiovascular targets extracted directly from literature mining (black marks) and the 421 additional proteins identified from cross-pharmacology relationships with those cardiovascular targets (white marks). The ordering of the ligands (from right to left) was done on the basis of having an annotation to the following families—CP: cytochromes P450; CY: cytokines; EC: general enzymes; aGR: aminergic GPCRs; pGR: peptidic GPCRs; oGR: other GPCRs; IC: ion channels; IN: integrins; KC: kinases; NR: nuclear receptors; TC: transporters.

tively. Note that since analyses based on ligand–target interaction data extracted from the literature are known to suffer strongly from data completeness issues [33], the values reported above should, in general, be considered as lower-bound estimates of the average degree of cross-pharmacology expected intrinsically from the different protein families.

In addition, many of the 44 032 small molecules connected to 160 cardiovascular targets were reported to have biological activities for proteins not originally present in the list of cardiovascular targets. Therefore, they constitute a valuable indirect source to infer the overall target space of relevance to cardiovascular drug discovery. In total, an additional set of 421 proteins was extracted, comprising 260 enzymes (including 42 proteases and 127 kinases), 69 ion channels, 66 GPCRs, 9 nuclear receptors, 8 cytokines, 6 transporters, and 3 integrins. Figure 4 shows the interaction map connecting the 14 734 scaffolds extracted from those 44 032 molecules (in columns) to all 581 targets (in rows) jointly organised in protein families. In this matrix, annotations to any of the 160 cardiovascular targets are given in black, whereas annotations to any of the 421 proteins recovered through cross-pharmacology relationships with any of the cardiovascular targets are given in white.

A total of 2058 connections between pairs of targets involving one cardiovascular and one cross-pharmacology target that share at least one bioactive ligand were identified. Again, the number of bioactive ligands in common between two targets varies significantly. While 52 target pairs have more than 100 bioactive ligands in common, 1802 have fewer than 10. Metalloendopeptidases (within enzymes) and aminergic GPCRs (within GPCRs) are among the families showing the highest degree of internal cross-pharmacology (see insets in Figure 4). In fact, out of the 10 cross-pharmacology targets having the largest number of common bioactive ligands to cardiovascular targets, 4 are aminergic GPCRs (namely, serotonin 5-HT_{1A} and 5-HT_{2A}, dopamine D3, and adrenergic α_{1D} receptors) and 2 are metalloendopeptidases (namely, MMP-1 and MMP-3/stromelysin 1).

Given the relatively high degree of cross-pharmacology observed previously among cardiovascular targets, it is tempting to presume that the relevance to cardiovascular events of some of the proteins identified indirectly through literature-based annotated compounds might be beyond mere phylogenetic relationships with cardiovascular targets. Accordingly, individual disease-directed searches [34] were performed to clarify the involvement in cardiovascular events of the 27 cross-pharmacology targets sharing with cardiovascular targets more than 100 bioactive ligands. Remarkably, recent association with cardiovascular events could be confirmed for 19 of those targets. Among them, one can find 9 aminergic GPCRs (namely, muscarinic M_5, adrenergic α_{1D}, dopamine D_1 and D_3, and serotonin 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2A}, and 5-HT_{2C} receptors), which together with the 17 present already in the original list of cardiovascular targets corroborate the relevance of this particular family in cardiovascular regulation [35,36]. The remaining 10 targets included 5 enzymes (namely, squalene synthetase, butyrylcholinesterase, MMP-1, MMP-3, and MMP-13) and 3 GPCRs (namely, neuropeptide Y1, μopioid, and tachykinin 2 receptors), in addition to the dopamine transporter and progesterone. These results highlight the use of annotated chemical libraries as an attractive strategy to complete the cardiovascular-relevant target space by connecting proteins through cross-pharmacology relationships.

Conclusions

In this work, a list of 233 proteins associated to cardiovascular events has been compiled, organised, and made available. Among those, a first set of 214 proteins was extracted directly from bibliographic sources and it was later completed with an additional set of 19 proteins identified from cross-pharmacology relationships derived from literature-based pharmacological data. In this respect, bioactive small molecules emerged as a precious indirect source to delineate the entire target space relevant to cardiovascular drug discovery. Annotated chemical libraries also played a key role to define the expected levels of cross-pharmacology within protein families. For example, the number of cross-pharmacology connections for aminergic GPCRs was found to be significantly higher than for nuclear receptors. One may anticipate that this information can be exploited to warn *a priori* on the higher risk for cardiovascular side effects associated with off-target promiscuities intrinsic to the nature of the protein family to which a particular cardiovascular target belongs.

Following recent trends in chemogenomics, the process of collecting prior information on protein structures and bioactive ligands available for all relevant cardiovascular targets and then organising all this target-focused information into protein families to generate family-oriented knowledge provides the basic framework for attempting to make global cardiovascular drug discovery efforts more efficient. The generation of this family-oriented knowledge may ultimately have an impact on a variety of activities, such as developing methods for the *in silico* cardiovascular profiling of large chemical libraries, applying them in cardiovascular-directed compound acquisition campaigns to augment corporate screening collections, or designing appropriate cardiovascular screening batteries to address selectivity issues beyond phylogenetic relationships. Expanding this chemogenomics view of cardiovascular drug discovery to other therapeutic areas may shed some light on our present understanding of the interplay between proteins and diseases and its ultimate translation into drug safety and efficacy.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.drudis.2009.02.010.

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