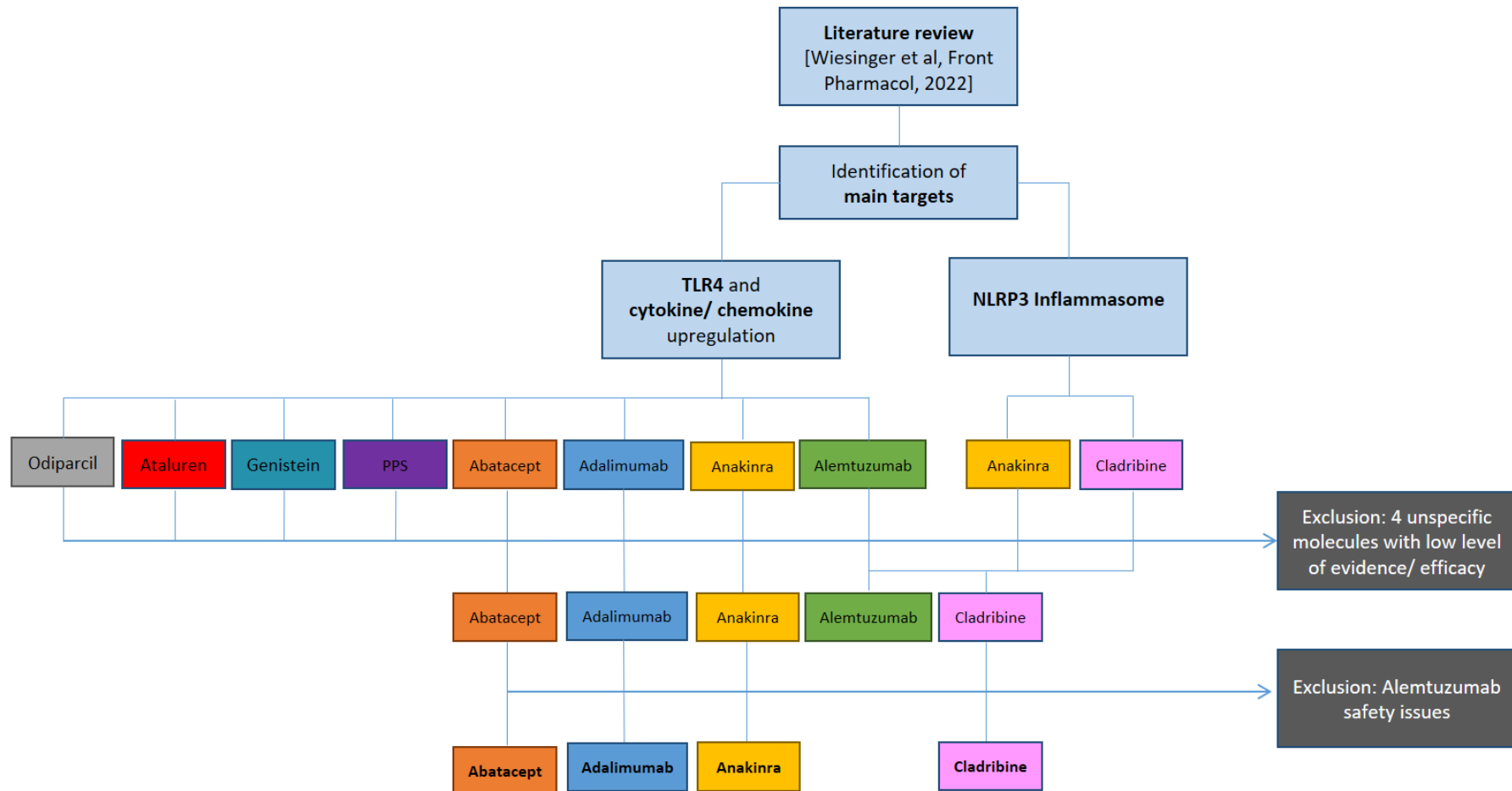


Data and Drug Selection:



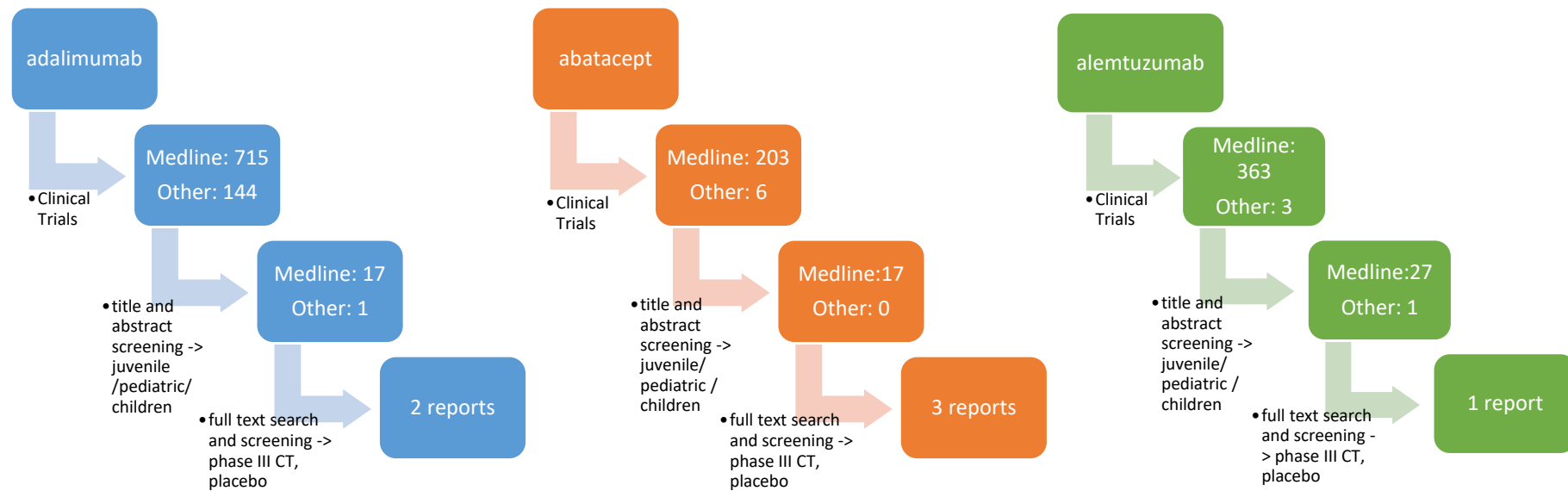
Data and Drug Selection:

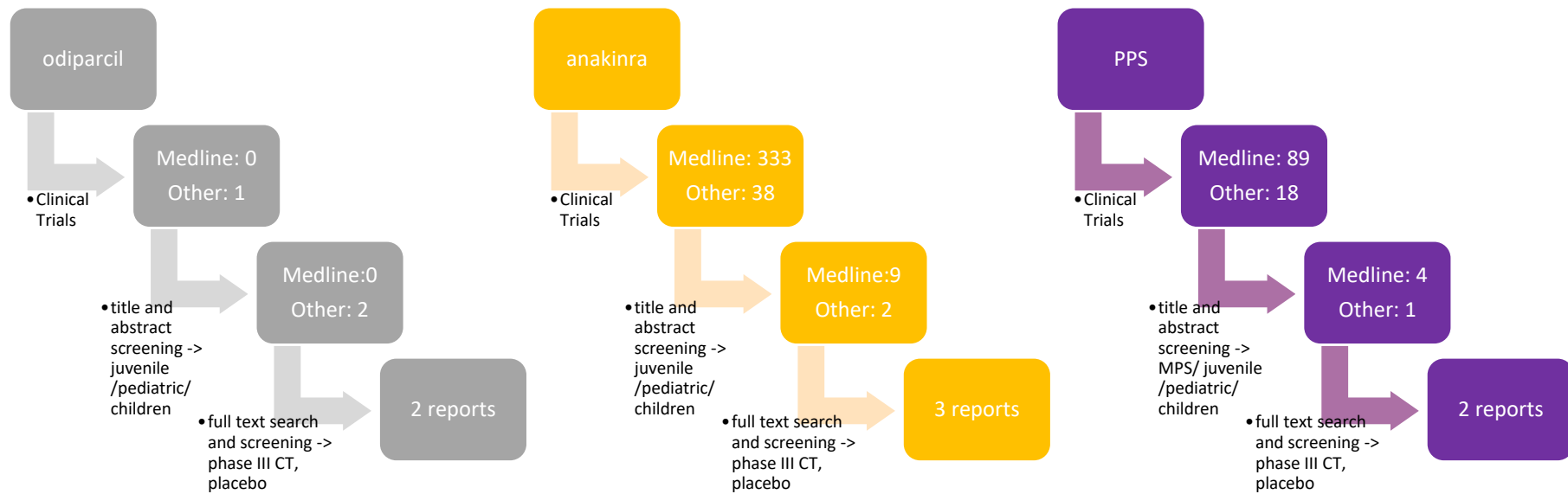
A comprehensive literature review on inflammation driven cell pathology in MPS [1] identified two main targets for intervening in the viscous circle of inflammation in MPS, namely (i) the TLR4 receptor and cytokine/ chemokine upregulation and (ii) the activation of the inflammasome NLRP3. This led us to 9 promising molecules: adalimumab, anakinra, alemtuzumab, pentosan polysulfate (PPS), ataluren, genistein, cladribine and odiparil.

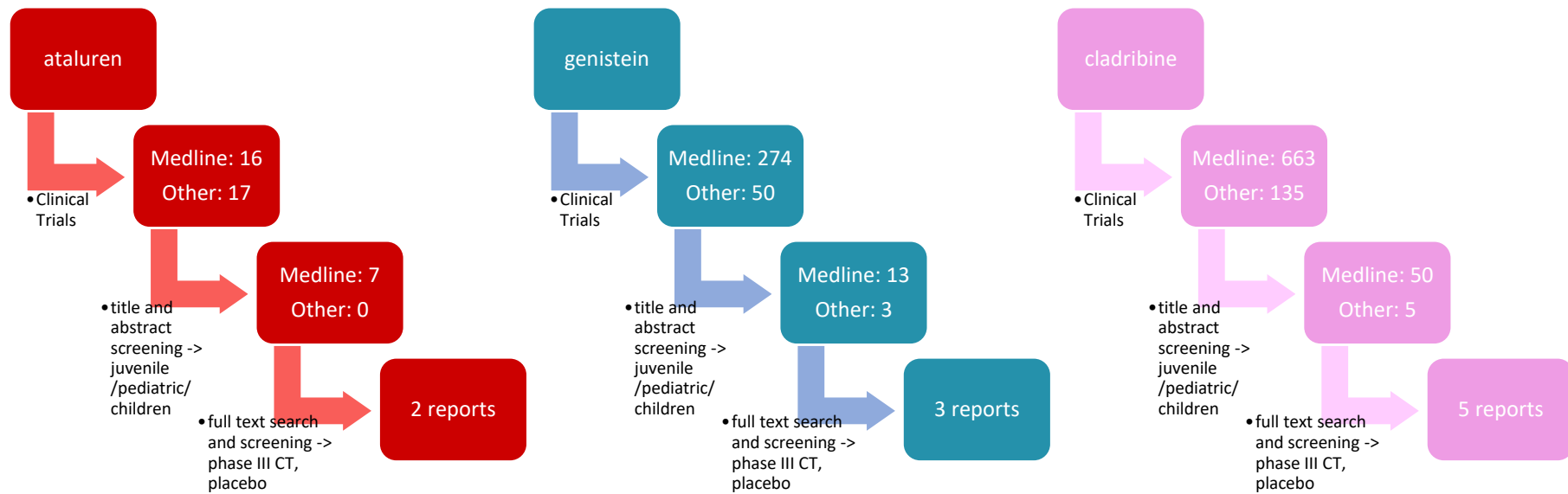
Afterwards, database searching via **Medline** and others (ClinicalTrials, Clarivate, SpringerLink) was performed for each drug using the same search strategy with a defined strict procedure. We searched for English-language reports of **i.) studies in MPS** (regardless of study type and design), **ii.) MPS case reports** and **iii.) phase III or IV randomized placebo-controlled pediatric clinical trials** with at least 12 weeks of treatment duration. This led us to an exclusion of 4 drugs (ataluren, genistein, odiparil, PPS) due to (i) an unexplained mechanism of action and (ii) a low level of evidence compared to the other molecules. Genistein was excluded despite a relatively high number of published studies (324 reports), due to the repeatedly reported low efficacy even in higher doses [2, 3].

Consequently, the remaining five molecules (alemtuzumab, anakinra, adalimumab, abatacept, cladribine) have been further assessed, using the structured, quantitative RBA also used by regulatory authorities [4]. The results of this assessment led the expert board to an exclusion of alemtuzumab due to safety issues [5-24].

By this, we selected the following candidates for integration into our model: anakinra, adalimumab, abatacept and cladribine.







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